The Journal of
CLINICAL
ENDOCRINOLOGY

VOLUME 3 JANUARY, 1943 NUMBER 1

Thyroidal Action of Synthetic Thyroprotein

E. P. REINEKE, PH.D., AND
C. W. TURNER, PH.D.[1]

From the Department of Dairy Husbandry, University of Missouri, Columbia, Missouri

DURING the past several years marked progress has been made in the production of synthetic thyroproteins with high physiologic activity. As the result of recent experiments in our laboratory a prodecure has been worked out whereby a product can be obtained which has several-fold the thyroidal activity of desiccated thyroid. While the primary objective of this work was to produce thyroidal material at a cost sufficiently low to warrant its use in feeding domestic animals, it would appear that with the attainment of that objective, a synthetic thyroprotein has been formed which may have important clinical uses not only because of the marked reduction in cost which would be possible, but also because of the uniform potency that would result from standardization of the manufacturing procedure and the biologic assay of large batches of material.

The purpose of this paper is to review briefly the history of the progress made in producing synthetic thyroproteins and to call to the attention of experimental clinical endocrinologists the character of the product now available.

Received for publication Oct. 13, 1942.

[1] Contribution from the Department of Dairy Husbandry, Missouri Agricultural Experiment Station Journal Series No. 866.

HISTORICAL BACKGROUND

The discovery of iodine in firm organic combination in the thyroid by Baumann (1) and the identification of thyroglobulin as an iodoprotein by Hutchinson (2), Oswald (3) and others, directed the attention of early investigators to the formation of iodoproteins by chemical means. From that time to the present numerous studies have been published both on the chemistry involved in the iodination process, and the physiologic properties of the iodoproteins thus obtained. By this means a considerable body of information was built up as to methods of combining iodine with proteins and the points of combination of iodine in the protein molecule. However, early tests for thyroidal activity of these products produced uniformly negative results. In view of our recent success in producing iodinated proteins with a high degree of thyroidal activity, it appears that these early attempts were un-

successful only because of the failure to establish the optimum conditions for the desired reaction to take place.

Hutchinson (4) prepared nucleo-albumins containing 4 to 7 per cent of iodine by iodinating the proteins extracted from calf thymus. These products were reported to be without effect when tested by administration to thyroidectomized dogs and myxedematous human patients. Following the iodination of thyroid colloid, Hutchinson was not able to discern any increase in thyroidal activity above that of natural thyroglobulin, even though the iodine content had been increased 10-fold.

Blum (5), on the basis of his early experiments, reported that his iodinated albumin had the same effects in myxedema as the thyroid. In later reports, however, he appeared to withdraw from that position, and denied that such preparations had any thyroidal activity. Similarly Wormser (6) tested the 'caseo-iodine' of Liebricht (7) on thyroidectomized dogs without effect, although administration of the same preparation to two goiter patients reduced the goiters and resulted in improvement of the patients.

A new technique for the detection and measurement of thyroidal activity was made available by the discovery of Gudernatsch (8) that thyroid substance will cause rapid and precocious metamorphosis of frog tadpoles. Using this test, Morse (9) reported that iodinated proteins produced effects which were comparable to those of desiccated thyroid. Lenhart (10) reported the effects on tadpoles of iodoalbumin, a commercial preparation of iodinated protein containing about 21 per cent iodine. Even though stimulation of metamorphosis was observed, it was also noted that the tadpoles all developed a disease resembling general body edema. In view of the large amount of loosely bound iodine in iodoalbumin, it was felt that the toxic effects of free iodine had to considered, and hence the results were not accepted as suggesting a thyroid-like action for this product. Rogoff and Marine (11) concluded that iodoalbin a commercial iodinated protein has an action on tadpoles similar to that of thyroid, but that the effect takes place more slowly. In further work, Rogoff and Marine (12) iodinated ox serum, serum globulin, serum albumin and egg white. They also tested commercial iodoalbumin (Merck) and iodocasein (Mulford). When these were administered to tadpoles some thyroidal activity was noted in all of the products tested. However, alkaline hydrolysis appeared to destroy the active principle in all of the preparations.

Following these early experiments, there was a lapse of more than 20 years in which little or no attention was given to possible thyroidal properties of iodinated proteins. Among reasons which may be advanced for this lapse of interest are the early failures to demonstrate a thyroidal response with various iodinated protein preparations when given to human patients, and also the fact that the tadpole assay, contrary to our present information, was believed to lack specificity. Therefore, the results obtained on tadpoles were generally attributed to a special property of this type of preparation rather than to a specific thyroidal effect. Furthermore, after the isolation of thyroxine by Kendall (13) and its synthesis by Harrington and Barger (14), it appeared extremely unlikely that a compound of this nature could be formed during the simple iodination of proteins, especially since no mechanism for such a synthesis was recognized in the field of organic chemistry.

Brandt, Mattis and Nolte (15) reported that they fed ordinary iodoproteins to tadpoles for as long as 4 weeks, with no acceleration of the rate of development above that of the controls. It was reported, however, that the acid-insoluble precipitate obtained after hydrolysis of iodoproteins with barium hydroxide showed an effect similar to that elicited by thyroid substance. Käer in 1934 (16) reported that the feeding of iodotropon, a commercial product, to frog tadpoles produced a response similar to that produced by thyroxine. The specificity of the tadpole test for thyroidal activity is supported in this case by the fact that although both sodium iodide and diiodotyrosine inhibited growth slightly, they had no effect on metamorphosis.

Considerable success in the concentration and purification of the thyroidal principle contained in certain iodinated proteins was reported by Abelin and his co-workers (17–21). When iodinated proteins were first hydrolyzed with alkali, an acid-insoluble precipitate was obtained which contained about 26 per cent

iodine and was designated as homo-thyroxine. Extensive tests of this substance indicated that it possessed, qualitatively, all of the physiologic properties of true thyroxine. Salter and Lerman (22) reported that when blood serum was iodinated in an aqueous ammonia medium and subsequently hydrolyzed with barium hydroxide, an acid-insoluble precipitate with thyroidal properties could be obtained. This material contained 24 per cent iodine, and was found to be effective in the relief of human myxedema. In further work, Lerman and Salter (23) reported that iodinated serum protein, as well as its acid-insoluble degradation products, was effective in the correction of myxedema in human patients and thyroidectomized rabbits.

Finally, Ludwig and von Mutzenbecher (24) announced the isolation of crystalline thyroxine from the barium hydroxide hydrolysates of iodoproteins which had been previously prepared under carefully controlled conditions. This important finding was fully confirmed by Harington and Rivers (25). Thus it was established beyond a doubt, that thyroxine can actually be recovered by the proper treatment of iodinated proteins of non-thyroidal origin. However, physiologic assays of iodoproteins before hydrolysis and concentration of the active principle had shown either negative results or a relatively low order of potency.

It appeared to the writers to be of considerable interest to attempt to devise a method of iodination and subsequent treatment of the protein in order to form a product with high activity, if possible, without further digestion and concentration of the thyroidal substance. With this objective in mind a systematic study was made of the effect of numerous variations in the iodination procedure on the thyroidal activity of the iodoproteins thus formed. A detailed account of the experiments performed with this objective in mind is being published elsewhere (26). Therefore, the present report will be confined to a description of the preparation now available, together with biologic tests of its thyroidal activity.

EXPERIMENTAL PROCEDURES

Assay methods. As a preliminary to testing the thyroidal potency of the large numbers of iodoprotein preparations which would be involved in determining the many factors which could conceivably affect their potency, it was necessary to adapt biologic assay methods for this purpose. In the earlier work the preparations were tested both by the stimulation of increased oxygen consumption of guinea pigs in response to a given dose of test substance, and by the stimulation of tadpole metamorphosis. Inasmuch as the two methods showed uniformly consistent results when tested on the same preparations, the more rapid and convenient tadpole test was used almost exclusively in the later work. By use of methods of induced ovulation of female frogs, and artificial insemination and incubation of the eggs, it was possible to maintain a stock of tadpoles for this work during most of the year. It was found that under our conditions of assay the injection of thyroxine or of active iodinated protein solutions would stimulate rapid metamorphosis, the percentage decrease in body length of the tadpoles varying as the logarithm of the dosage. No response of the kind was given by the injection of either diiodotyrosine or potassium iodide. It is believed, therefore, that, as used in our laboratory, the tadpole assay is fairly specific for thyroidal effects. It was also established that preparations of iodinated protein which would produce 1 per cent of the effect of thyroxine when administered orally to guinea pigs would elicit about 2.7 per cent of the response of thyroxine when both preparations were injected into tadpoles. Thus from a given tadpole assay, it is possible to predict the relative effect which would be produced by the oral administration of such preparations to guinea pigs and probably other mammalian forms.

Factors affecting thyroidal activity. Among the factors studied with regard to their effect on the thyroidal activity of the resulting products were, *a*) the concentration of sodium bicarbonate in the iodination medium, *b*) the amount of iodine combined with the protein, and *c*) the temperature at which the iodination and incubation processes are carried out.

When the sodium bicarbonate concentration of the iodination medium was increased progressively in succeeding preparations, all other factors being held constant, it was found that thyroidal activity reached the maximum when sufficient bicarbonate had been added to maintain the pH of the reaction mixture within the range of 6.8 to 8.0. Addition of an excess of bi-

carbonate beyond this amount had no measurable effect on thyroidal activity.

When the concentration of bicarbonate was held within the optimal range and the iodine input was varied, the amount of iodine added to the mixture was found to be a limiting factor (27). It was found that the thyroidal activity of the resulting products increased progressively with increasing iodine concentration until sufficient iodine had been added to substitute 2 atoms per molecule of tyrosine in the protein used. Iodination beyond that point led to significant losses in thyroidal activity, thus differing markedly from the results reported by Muus, Coons and Salter (28) by use of a different iodination medium.

Extensive assay of preparations made up with both the sodium bicarbonate and iodine concentrations held within the optimal range thus established showed them to exert a thyroidal effect equal to 1 per cent of that of thyroxine when tested by oral administration to guinea pigs and about 2.7 per cent of the thyroxine response when injected into frog tadpoles. Comparative assays indicated that these products were somewhat more active per unit of weight than U.S.P. thyroid powder when tested by the same mode of administration in guinea pigs.

In previous work on the iodination of proteins the reaction had been carried through at various temperatures by different workers, but no one had thus far investigated the effects of the reaction temperature on the thyroidal activity of the resulting products. It appeared to be of considerable interest, therefore, to maintain the amount of added iodine and bicarbonate at the optimal levels established, and to study the effect of progressively increasing temperature on the amount of thyroidal principle formed. A series of preparations was made up in which the temperature of the reaction mixture was increased progressively through the range of 30 to 97° C. Assay of these preparations showed little change in activity within the range of 30 to 45° C. With increase of the temperature to 60°, however, there was a striking increase in thyroidal potency which reached a maximum at approximately 70° C. Furthermore, it was discovered that this increase in activity would take place as well if the iodine was first combined at the usual temperature of 38° C., and the mixture then incubated at 70°, as if both steps of the process were carried out at the elevated temperature. Repeated assay of these recent preparations shows about a 4-fold increase in thyroidal activity over that of products made up at the usual temperature of 38° C. Thus these preparations show thyroidal activity of about 4 per cent that of thyroxine when assayed by oral administration to guinea pigs or approximately 11 per cent of the thyroxine response when injected into tadpoles.

The optimal concentration for maximum thyroidal activity when casein is used as the substrate has been found to be about 7 ± 2 per cent. After the incubation at elevated temperature there is no appreciable change from this iodine content in the resulting product. It appears, therefore, that the increased potency must be due to increased formation of the active principle, rather than a hydrolysis and concentration of this factor. This is believed to indicate, further, that the active substance remains combined within the protein molecule. Thus the results must be clearly distinguished from those of Lerman and Salter (23) in which they reported the recovery of a peptide with a 20-fold increase of activity in relation to its iodine content following the hydrolysis with barium hydroxide of an iodoprotein formed by the iodination of serum in an ammoniacal medium.

It is noteworthy that these preparations of iodinated protein of non-thyroid origin show extremely high thyroidal activity when tested by injection as well as by oral administration. This raises the question whether such artificial thyroproteins exert their effect as such or whether they are first broken down within the organism and then reconstituted into an active molecule. Although little work with regard to this interesting point has been done on mammalian test animals, Koger (29) has found one of these products to be effective when injected subcutaneously into mice, and indeed the same relationship appeared to hold as that previously noted in the comparative assays on tadpoles and guinea pigs. That is, when expressed in relation to the response to thyroxine, iodinated

protein injected into mice is 2.7 times as active as when given orally.

The question arises whether the thyroidal effects observed are actually due to the formation of thyroxine or to some other compound or state of combination in the protein. In a previous report (30) we have shown that artificial thyroproteins such as those reported upon herein, will completely prevent the development of cretinism in thyroidectomized goats, and when given at the required dosage level will stimulate growth approaching the normal. It is of particular interest that during nearly a year of continuous feeding of thyroprotein to these animals no toxic effects or undesirable symptoms that could be attributed to the treatment have been noted.

The administration of this artificial thyroprotein to cows and goats (31) induced increases in milk production and the percentage of milk fat was similar in every respect to the responses noted previously upon the administration of desiccated thyroid (32) or thyroxine (33).

Added to these physiologic effects is the fact that thyroxine can be isolated readily from this synthetic thyroprotein subsequent to hydrolysis with barium hydroxide by the procedure of Ludwig and Mutzenbecher (24). In a recent experiment (unpublished) we have applied this procedure to a highly active preparation of iodinated protein prepared under the optimum conditions described previously.[2] From 100 gm. of this product we were able to isolate 424 mg. of crystalline thyroxine in a state of high purity. Thus, in spite of the sizeable losses of thyroxine involved in this isolation procedure, we obtained an actual yield of more than 0.4 per cent of crystalline thyroxine. This is more than 3 times the analytical value for thyroxine which is normally obtained with thyroid powder containing 0.2 per cent iodine. By biologic assay the crude iodinated protein preparations have shown at least 4 times the thyroidal activity of a commercial thyroid powder with which they were compared.

[2] We are indebted to Dr. W. R. Graham, Jr., of the Cerophyl Laboratories, Kansas City, Mo., for supplying a generous amount of this preparation that had been made up according to our procedure. This firm is now able to supply a highly active artificial thyroprotein for experimental or clinical use.

COMMENT

In view of the results outlined in this paper, it is believed that the experimental basis for the production of highly active artificial thyroproteins is firmly established. By controlling the production process so that all of the important factors governing the activity of the product are held within the optimal range it is now possible to prepare consistently an iodinated protein which has many times the activity of thyroid powder, as judged either by its biologic assay, or by the actual yield of crystalline thyroxine which can be recovered from it.

The material is active when given orally, and in experimental animals it has also been found to be highly active by subcutaneous injection. Although one would expect to obtain eventually a protein sensitization of animals injected with a material of this nature, no untoward reactions have been noted following its daily injection in mice over a period of several weeks. In this connection it is interesting to note that Wormall (34) reported that proteins lose their antigenic specificity when iodinated and acquire a new specificity for iodoprotein.

In all respects in which these preparations have been tested biologically thus far, they exert an effect that is indistinguishable, qualitatively, from that of thyroxine or thyroid substance. It would be of considerable interest to determine the relative effect of artificial thyroproteins on the elevation of the metabolism and heart rate, as compared to the same relative effects of thyroid substance. Meyer and Danow (35) reported that they were able to prepare from thyroid a substance which showed considerably less stimulation of the heart rate for a given increase in metabolism than did whole thyroid. A similar effect was noted for a 'T' peptone recovered from a hydrolysate of iodinated serum albumin(36). Lerman and Salter were not able to detect any significant difference in the heart rate or blood pressure produced by iodoproteins as compared with natural thyroid or thyroglobulin. In our tests of artificial thyroprotein preparations on ruminants, it has appeared from records of the heart rate, the relative increases in milk production and subjective observations that these products also produce a relatively smaller

stimulation of the heart for a given increase in metabolic response than was observed in earlier work with desiccated thyroid and thyroxine. More exact quantitative measures will be required, however, to verify this point.

Salter and Lerman and their co-workers (22, 23, 28) have pioneered in testing clinically the calorigenic effects of iodinated serum albumin and its degradation products. The preparations with higher physiologic activity which we have been able to produce through close attention to the critical factors affecting their formation are now available for further clinical experimentation.

SUMMARY

Experiments leading to the chemical formation of artificial thyroproteins with high thyroidal activity are described. Critical factors in the formation of such preparations are the degree of iodination of the protein, the pH of the reaction medium, and the temperature at which the iodination and incubation processes are carried out. Products formed under optimal conditions have several times the thyroidal activity of standard thyroid powder as judged either by their biologic assay or by the yield of crystalline thyroxine which can be obtained from them subsequent to hydrolysis. The material is now available for clinical trial.

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Effects of Various Thyroid Substances in Patients with Obesity

S. WILLIAM KALB, M.D.

From the Nutrition Clinic, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University

THE CLINICAL picture of thyrotoxicosis with its manifestations of generalized increased body metabolism and circulatory activity is well recognized. So, too, prolonged medication or overdosage with thyroid substances administered for therapeutic purposes may cause the appearance of such signs and symptoms of toxicity as palpitation, nervousness, diarrhea, tremors, weakness and increased diaphoresis. Rasmussen (1) demonstrated that long-continued administration of desiccated thyroid gland to dogs, *a*) produced paroxysmal tachycardia, *b*) augmented the systolic blood pressure, *c*) caused electrocardiographic changes (negative T waves or prolonged QT intervals) and *d*) finally death by circulatory insufficiency. In human subjects receiving thyroid therapy, acute dilation of the heart, angina, left heart failure (2), cardiac involvement such as that seen in Addison's disease (3) and auricular fibrillation (4) have been described. Salter (4) warned against overtaxing the physiologic reserves of the heart and adrenal cortex specially in the aged or myxedematous patient by excessive thyroid administration.

In obese individuals, thyroid substances have been employed along with low-caloric diets to aid in accelerating weight loss. Handelsman and Gordon (5) using thyroprotein containing 0.4–0.6 per cent iodine showed that weight loss could be increased when diet alone became ineffective. Lyon and Dunlop (6) as well as Bayer and Gray (7) also concluded that thyroid is useful in weight reduction. Grafe (8) and Handelsman and Gordon (5) were of the opinion that irrespective of the basal metabolic rate, obese individuals responded to thyroid administration as did normal subjects. Sollman (9) and Goodman and Gilman (10) emphasized the circulatory complaints and other toxic reactions which may be experienced by obese individuals on thyroid therapy.

In the treatment of obesity it would seem advantageous to utilize the calorigenic property of desiccated thryroid substance if the disturbing effects of increased cardiac activity could be eliminated. Meyer and Yost (11) observed in thyroidectomized rats that commercial dried thyroid substance caused a definite increase in heart rate, while a purified thyroglobulin fraction maintained its calorigenic properties without comparable cardiac effects. Thyroglobulin has also been employed in the treatment of menstrual irregularities (12) and although it was no more beneficial than desiccated thyroid in the treatment of this disorder, it had the added advantage of not causing nervousness and palpitation, disturbances which were noted with the use of desiccated thyroid.

In the present study, thyroglobulin as well as other commercial thyroid preparations were prescribed for obese individuals to supplement low-caloric diets as an aid to accelerating weight loss.

METHOD

There were two groups of obese patients studied. Each was on a sub-maintenance diet. The first group consisted of 469 patients; 169 were given thyroglobulin;[1] 100, Parke, Davis'

Received for publication October 16, 1942.

[1] Thyroglobulin (Proloid) was supplied through the courtesy of the Maltine Co., Brooklyn, N. Y.

TABLE 1. RESPONSE OF OBESE PATIENTS TO THYROID SUBSTANCES

Group	Number of Patients	Pulse Rate Arithmetic Mean at End of Observations	Standard Deviation	Probable[2] Error of Mean	Significant Difference[3]	Ratio[4] Control to Medication	Pulse Change[5] percentage	
							Increase	Decrease
Control	100	79	7.13	0.48	0	1:00	72	28
Thyroglobulin	169	79	7.96	0.41	0.95	1:1.11	92	8
Armour's thyroid	100	78	14.33	0.97	1.60	1:2.01	93	7
Parke, Davis' thyroid	100	79	14.67	0.99	1.63	1:2.06	91	9

[1] Standard deviation $\sigma = \sqrt{\frac{\Sigma(d^2)}{N}}$.

[2] Probable error of mean $= 0.6745 \frac{\sigma}{\sqrt{N}}$.

[3] $\frac{m_1 - m_2}{\sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}}$.

[4] $\frac{\text{Standard deviation}}{\text{Standard deviation of the control}}$.

[5] Percentage of patients showing increase or decrease over initial pulse rate.

thyroid; 100 Armour's thyroid; 100 were given placebos. Each thyroid substance was given in doses of 1 grain 3 times a day for 2 to 32 weeks; the drug was discontinued when toxic manifestations occurred. At every clinic visit, the pulse rate, blood pressure and the toxic manifestations if any, were recorded.

The second group comprised 45 obese individuals. All of these received a low-caloric diet but no medication for 4 weeks, during which period the patient was weighed and the pulse and basal metabolic rate were noted; these data served as control observations. Following this initial period, 5 subgroups of 8, 11, 16, 7 and 3 patients, respectively, were given the following thyroid substances: thyroglobulin, Parke, Davis' thyroid and Armour's thyroid, in doses of 1 grain 3 times a day for 4 weeks. The basis for forming the sub-groups was the sequence in which each of the thyroid substances was administered.

TABLE 2. EFFECT OF DAILY ADMINISTRATION OF 3 GRAINS OF THYROID SUBSTANCES FOR TWO TO THIRTY-TWO WEEKS ON ARTERIAL BLOOD PRESSURE

Thyroid Substance	Number of Patients	Average Change of Blood Pressure	
		Systolic	Diastolic
Thyroglobulin	169	−1	−2
Parke, Davis'	100	−2	−2
Armour's	100	−2	−2
Control	100	−1	−1

RESULTS

Table 1 shows a statistical analysis of the effect of various thyroid substances on the pulse rate. This protocol indicates that the thyroid substances used in the dosages already mentioned were without significant effect on the cardiac rate. Thus, in each instance the difference between the means of the pulse rate in the normal group and the various thyroid groups divided by the standard error of the difference of these means gave values less than 3, indicating the lack of statistically significant variations.

Table 2 indicates the effect of thyroglobulin, Parke, Davis' and Armour's thyroid and placebos on blood pressure. It is evident that none of the thyroid substances caused a change in either systolic or diastolic blood pressure.

Table 3 represents the incidence of side effects and toxic manifestations caused by the various thyroid substances. With the exception of palpitation (18 to 20%), relatively few toxic reactions were experienced; no difference was observed in this respect between the various thyroid substances. Increased cardiac rate

TABLE 3. INCIDENCE OF TOXIC MANIFESTATIONS CAUSED BY DAILY ADMINISTRATION OF 3 GRAINS OF THYROGLOBULIN TO 169 PATIENTS, PARKE, DAVIS' THYROID TO 100 PATIENTS AND ARMOUR'S THYROID TO 100 PATIENTS FOR TWO TO THIRTY-TWO WEEKS

Symptoms	Thyroglobulin %	Parke, Davis' Thyroid %	Armour's Thyroid %
Tachycardia	5.1	16.0	12.0
Headaches	3.4	8.0	9.0
Dizziness	3.4	1.0	0.0
Palpitation	20.2	19.0	18.0
Weakness	6.7	7.0	3.0
Nervousness	8.5	8.0	9.0
Diaphoresis	3.4	5.0	1.0

TABLE 4A. EFFECT OF DAILY ADMINISTRATION OF 3 GRAINS OF EACH OF THREE THYROID SUBSTANCES FOR 4-WEEK PERIODS IN THE INDICATED ROTATION ON WEIGHT LOSS, PULSE RATE AND BASAL METABOLIC RATE (8 patients)

Original Weight lb.	Final Weight lb.	Weight Loss lb.	No Medication		Thyroglobulin		Armour's Thyroid		Parke, Davis' Thyroid	
			Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.
181	147	34	78	+15	78	+31	84	− 7	96	+ 3
212	153	59	90	− 3	90	+ 7	84	+12	96	− 2
125	110	15	84	−16	84	+ 2	84	− 3	84	− 1
147	131	16	84	−17	84	+ 2	84	− 2	90	− 6
129	115	14	84	−10	84	0	84	−17	84	− 1
141	115	26	72	−17	90	−20	84	−19	84	−10
206	183	23	72	−18	78	−12	80	− 2	84	− 9
169	137	32	72	−18	84	+12	90	− 1	96	+ 3
Averages 164	136	27	79	−10	84	+ 3	84	− 5	89	− 3

(over 100 beats per minute), however, appeared to be a more frequent observation in patients receiving Parke, Davis' or Armour's thyroid than in those given thyroglobulin.

Tables 4A, B, C, D, and E demonstrate weight loss, pulse and basal metabolic rates after the administration of 3 grains of thyroglobulin, Armour's or Parke, Davis' thyroid daily for 4-week periods. These substances were administered in different time-relationships to each other in order to determine if the results produced by a given thyroid substance could be duplicated.

These tables show that a low-caloric diet supplemented by thyroid substances, regardless of the order of rotation, is followed by a loss of weight ranging from 19 to 46.2 pounds per patient over a period of 18 weeks. In general, the pulse rate was accelerated in over 90 per cent of the patients by each of the thyroid substances used. With regard to the effect on the basal metabolic rate, the results were equivocal. In practically all instances, each of the thyroid substances caused an increase in basal metabolic rate to the same degree. At times, one had a greater effect than the other, while at other times, either of the other thyroid substances could be used to maintain the increased basal metabolic rate.

DISCUSSION

Although the various thyroid substances used in this present study were shown to have exerted different calorigenic effects, the action

TABLE 4B. EFFECT OF DAILY ADMINISTRATION OF 3 GRAINS OF EACH OF THE SAME THYROID SUBSTANCES FOR 4-WEEK PERIODS IN THE INDICATED ROTATION ON WEIGHT LOSS, PULSE RATE AND BASAL METABOLIC RATE (11 patients)

Original Weight lb.	Final Weight lb.	Weight Loss lb.	No Medication		Thyroglobulin		Parke, Davis' Thyroid		Armour's Thyroid	
			Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.
189	162	27	72	− 8	90	−13	84	+22	84	−17
146	125	21	72	−25	84	− 4	80	− 4	84	− 4
186	167	19	70	− 2	76	−14	80	− 4	84	−10
93	78	15	80	+ 2	84	+10	90	+ 7	96	− 1
156	127	29	78	−24	84	−19	96	− 7	96	− 9
176	161	15	78	−15	98	+ 3	96	−14	96	−11
149	128	21	72	− 9	80	− 4	96	+ 1	110	+ 2
135	117	18	78	−27	84	−22	90	− 1	90	−10
135	122	13	70	−12	72	− 8	72	− 9	76	−14
141	124	17	72	−10	72	+ 1	78	+15	84	− 2
165	150	15	72	−32	90	−17	96	−21	84	−22
Averages 152	133	19	74	−15	83	− 8	87	− 1	90	− 9

TABLE 4C. EFFECT OF DAILY ADMINISTRATION OF 3 GRAINS OF EACH OF 3 THYROID SUBSTANCES FOR 4-WEEK PERIODS IN THE INDICATED ROTATION ON WEIGHT LOSS, PULSE RATE AND BASAL METABOLIC RATE (16 patients)

Original Weight lb.	Final Weight lb.	Weight Loss lb.	No medication		Parke, Davis' Thyroid		Thyroglobulin		Armour's Thyroid	
			Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.
212	178	34	72	−18	90	−23	78	−23	84	−22
199	178	21	72	−12	84	−11	90	−20	96	− 0
223	185	39	70	+16	84	+19	70	+37	78	+18
152	136	16	70	− 1	102	−11	84	+ 7	88	−15
189	164	25	96	−24	90	− 8	84	− 2	84	− 6
249	220	29	76	− 9	80	− 1	72	− 4	80	+ 2
175	151	24	78	−18	110	+10	96	− 1	96	−12
202	153	49	78	−18	96	− 1	96	+12	90	−17
164	154	10	72	−20	100	+ 3	90	− 3	96	− 4
174	141	33	84	−20	96	− 3	96	+ 2	100	− 5
152	124	28	72	− 7	90	+24	84	+12	84	+ 9
292	218	74	78	− 4	96	+34	90	+30	96	+22
172	148	24	66	+ 3	76	+10	72	+ 1	70	+ 4
161	130	31	80	− 5	96	− 3	78	+ 7	84	+29
169	136	33	72	−12	96	+15	78	+11	84	+ 8
235	206	29	84	+ 5	96	+21	96	+ 0	90	+ 5
Averages 195	164	31	76	− 9	93	+ 5	85	+ 4	88	+ 1

TABLE 4D. EFFECT OF DAILY ADMINISTRATION OF 3 GRAINS OF 3 THYROID SUBSTANCES FOR 4-WEEK PERIODS IN THE INDICATED ROTATION ON WEIGHT LOSS, PULSE RATE AND BASAL METABOLIC RATE (7 patients)

Original Weight lb.	Final Weight lb.	Weight Loss lb.	No Medication		Parke, Davis' Thyroid		Armour's Thyroid		Thyroglobulin	
			Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R
162	130	32	90	+16	120	+ 8	96	− 4	90	+ 3
151	129	22	72	−18	90	− 5	84	− 7	84	+ 9
166	139	27	60	− 7	84	−12	80	−15	90	+ 3
124	113	11	78	− 7	96	− 6	84	+15	78	−11
202	154	48	78	−18	94	− 1	90	+12	92	−17
282	183	99	80	− 5	120	− 2	96	+ 4	84	− 2
179	148	31	78	−32	110	− 5	84	−15	96	−12
Averages 181	142	38	76	−10	102	− 3	88	− 1	88	− 4

TABLE 4E. EFFECT OF THE DAILY ADMINISTRATION OF 3 GRAINS OF EACH OF 3 THYROID SUBSTANCES FOR 4-WEEK PERIODS IN THE INDICATED ROTATION ON WEIGHT LOSS, PULSE RATE AND BASAL METABOLIC RATE (3 patients)

Original Weight lb.	Final Weight lb.	Weight Loss lb.	No Medication		Armour's Thyroid		Thyroglobulin		Parke, Davis' Thyroid	
			Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.	Pulse rate per min.	B.M.R.
172	147	25	78	− 6	84	− 9	78	+29	84	+33
186	134	52	90	− 5	84	+ 9	72	+23	84	+13
225	164	61	76	−14	78	−23	78	−10	90	+ 0
Averages 195	148	46	81	− 8	82	− 8	76	+14	96	+15

of each on pulse rate was not dissimilar. It is generally conceded that the iodine content of a given thyroid substance determines its calorigenic-stimulating properties. Palmer and Leland (12) and Foster, Palmer and Leland (13) showed that the degree of metabolic stimulation by thyroid substances was quantitatively dependent upon the amount of *l*-thyroxin present. These observations were confirmed by other workers (14–17). A number of investigators (18–22), however, demonstrated that the iodine content of desiccated thyroid gland was a satisfactory index of its calorigenic activity.

This may be accounted for by the fact that the iodine content of the normal desiccated thyroid gland is a fixed quantity in relation to the total iodine content. It follows, therefore, that the concentration of iodine in a given thyroid preparation is demonstrated by the present studies and denotes its efficacy in increasing the metabolic rate. However, the effect on the pulse rate cannot be gauged by the iodine content of the thyroid preparation used.

Insofar as the study of weight loss in the obese patient is concerned, no further comment need be made other than that a definite weight loss was observed. In a previous publication from this clinic (23), it was concluded that desiccated thyroid alone, or in combination with amphetamine (benzedrine) sulfate failed to increase the rate of weight loss over that resulting from the submaintenance diet alone.

In general, toxic symptoms were not prominent except in the indicated instances. In another report from this clinic (24), it was pointed out that many of the symptoms such as headaches, weakness, palpitation and nervousness were observed in a significant number of obese patients who were on low-caloric intake alone. The figures for toxic symptoms attributable to thyroid reported here, therefore, may be too high.

SUMMARY AND CONCLUSIONS

1. Thyroid substances administered in doses of 180 mg. (3 grains) daily produced no change in either systolic or diastolic blood pressure in obese patients.

2. The administration of thyroid substances resulted in cardiac acceleration, but the effect on the pulse rate of the various preparations used was not dissimilar.

3. Relatively few toxic manifestations were noted; palpitation was the most common.

4. The administration of thyroid substances resulted in an increase in the basal metabolic rate. Parke, Davis thyroid appeared to be the most calorigenic, Armour's thyroid the least and thyroglobulin occupied an intermediary position.

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Treatment of Gigantism: Observations on a Pituitary Giant for Six Years

LEWIS M. HURXTHAL, M.D.

From the Department of Internal Medicine, The Lahey Clinic, Boston, Massachusetts

THE STATEMENT, 'gigantism is acromegaly of early life,' was made by several observers from 1892 to 1895 (1). Although enlargement of the pituitary fossa with pituitary tumor was described in earlier accounts of acromegaly (Saucerotte, 1772, gave the first medical description of acromegaly; Verga, 1864, first recorded autopsy) (1), Marie is given credit for establishing acromegaly as a definite disease entity (2). In a review of 34 cases of gigantism in 1897 Sternberg (3) showed that 14 cases had acromegalic alterations. Hutchinson (4) in 1900 found pituitary enlargement in 44 of 48 autopsies on acromegalic individuals. Thus this relationship between acromegaly, gigantism and pituitary tumor was recognized quite early and, although in the past some writers have not accepted it, it is generally recognized today.

Acromegaly has been described in childhood but such case reports as I have been able to find are not convincing. Acromegalic features, that is, widening of the hands and feet and disproportionate lengthening of the jaw, become more pronounced when final stature is approached.

There are many variables which determine the ultimate height reached by a giant. The height of the parents might influence the final stature. Nutrition or systemic diseases might play a rôle just as they do in growth of normal individuals. The duration of the hyperpituitary state, the age of onset, the time of epiphyseal closure, the hypersecretion or hyposecretion of other pituitary hormones might augment or retard growth rate.

Overactivity of the growth process may begin very early. Fetal giants weighing 10,000 gm. have been described (5). Schereschewsky (6) described a giant who finally reached a height of 283 cm. (9 ft. 2 in.) and was as tall as his 2-year-old brother at the age of 8 months. Our patient at the age of 5 years, according to school records, was slightly above average height and this became increasingly noticeable as time went on. At the same age the Alton giant had reached the height of 5 ft. 4 in. (7, 8). Growth proceeds at a fairly constant rate as judged by the plotted curves of available records. Growth should cease if sexual maturity takes place, because epiphyseal closure occurs then.

Giants differ greatly in other features. As in the case reported here, there may be evidence of excess of growth hormone only, with absent sex development and no indication of overactivity from other pituitary principles. Some giants appear normal in other respects, that is, they have attained full sexual development and have been able to procreate (9, 10). Some have been renowned for their great strength, although this was probably not in excess of their muscular development. Others have shown enlarged thyroids, diabetes, diabetes insipidus, hypertension, enlarged hearts with final dropsy, marked kyphosis, knock knees, flat feet, bony exostoses, weakness, anemia and so forth. These differences may be explained,

Received for publication September 3, 1942.

perhaps, by the numerous possible general and local effects of a functionally overactive and expanding pituitary tumor in its location in the sella turcica. Direct pressure on other pituitary cells, or on their blood and nerve supply, may or may not take place, and although the majority of these tumors are acidophilic in nature, there are probably other types of cells present in some cases. Overactivity may cease and regression of the tumor may take place, allowing normal pituitary tissue to resume its activities. Spontaneous decompression by rupture into adjacent spaces has been known to take place (11).

McFarland, as well as others, has collected data concerning height of various giants (12).

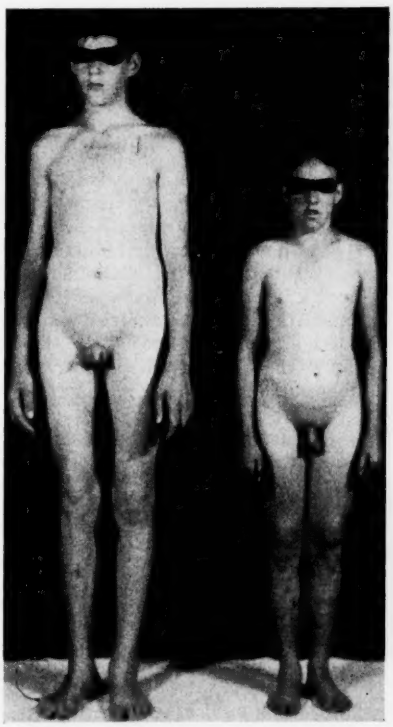

FIG. 1. PATIENT AT 15 YEARS OF AGE, when first seen July, 1936, standing beside a normal boy of average height, and same age.

Robert Wadlow, who died in 1940, reached the height of 272 cm. (8 ft. 10 in.) and is probably the tallest giant whose measurements cannot be questioned (13).

Gigantism presents not only a medical problem but also economic and social problems. An attempt to retard or arrest growth should be undertaken; sexual maturity is undoubtedly desirable and necessary to accomplish this end.

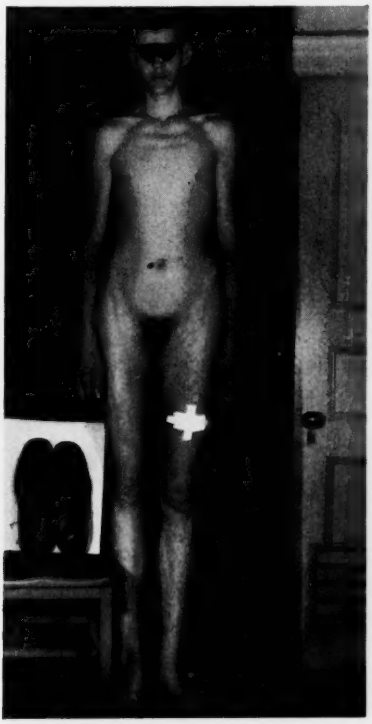

FIG. 2. PATIENT, APRIL, 1942. Compare height of patient to height of door. Gauze dressing covers site of pellet implantation. Patient's shoes are shown. Note toe deformities from wearing shoes which are too small.

Orthopedic problems arise from bearing excessive weight before bones have fully matured, or from hypertrophic bone changes in feet, knees or spine. Obtaining shoes which are large enough and will remain so is difficult and expensive, not to mention the matter of clothes. The type of occupation is limited and the social problem occasioned by being conspicuous is a handicap.

CASE REPORT

The patient was 15 years of age at the time he was first seen at the Clinic in July, 1936 (fig. 1 and 2). He was referred for examination because of rapid growth, having grown 6 inches during the previous 6 months.

At birth he weighed 7¾ pounds; he was taller than average at the age of 4 and 5 years and was much taller

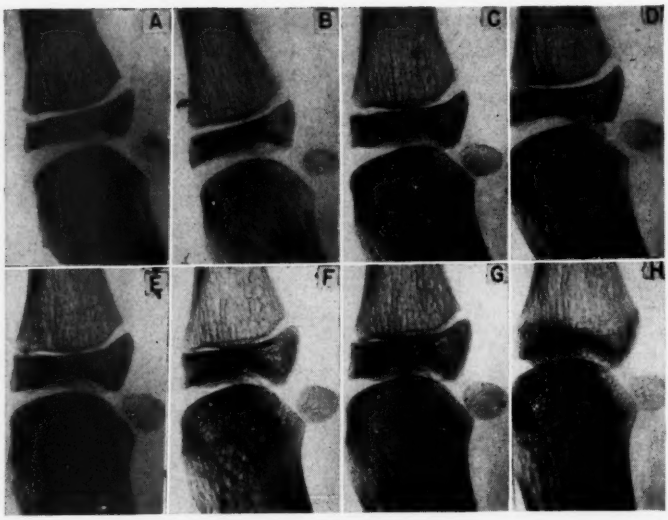

FIG. 3. EPIPHYSEAL CLOSURE. First metacarpal phalangeal joint, showing epiphyseal state at various stages: A, B, C. During roentgen-ray treatment over pituitary; July, 1936, to December, 1938; no other therapy. D, E. During roentgen-ray treatment plus gonadotropic and chorionic hormone treatment December, 1938, and September, 1939. F. Six months after cessation of gonadotropic and chorionic hormone treatment, July, 1940. G. At time of first testosterone pellet implantation January, 1941. H. Sixteen months after continuous treatment with testosterone pellets, April, 1942.

than his older brothers and sisters. He did fairly well in school but did not learn quickly.

On examination he was found to be 6 ft. 6.25 in. tall, weighed 190 lb. and had a span of 76.5 inches. The measurement from the pubic bone to the floor was 40 inches. He wore a size 16 shoe. He was slightly stooped. There was some widening of the facies suggesting early acromegaly. The skin was rather pale with many freckles over the face. The head hair was long, coarse and dense. There was no facial, axillary or pubic hair. The penis and testes were small, and the prostate was not felt.

The patient had been unable to get shoes sufficiently large so that hammer toes and corns had developed early.

The visual fields were entirely normal and the visual acuity was normal before treatment and has remained so up to the present time. Examination of the optic disks revealed normal findings; the blood pressure was 112 mm. Hg systolic and 75 diastolic. An audiogram showed normal hearing.

LABORATORY FINDINGS

The hemoglobin varied from 70 to 79 per cent during the 6-year period of observation. The highest red blood cell count was 4,470,000 and the lowest 3,400,000 over the same period. Blood cholesterol values never exceeded 170, the lowest being 133 mg. per 100 cc.

In 1936 the glucose tolerance test showed a fasting blood sugar of 69 mg. per cent, 72 at one-half hour; 107, one hour; and 79, two hours. In April, 1942, it was 94 mg. per cent, fasting; 132, one-half hour; 104, one hour; and 122, two hours. The non-protein nitrogen value was 20 to 23 mg. and the basal metabolic rate, −19 and −22 per cent, in July, 1936., before treatment. In 1942 the non-protein nitrogen was 31 mg. The water test for adrenal insufficiency (14) was normal in that one of the morning specimens (475 cc.) was greater than the night specimen (360 cc.)

ROENTGEN-RAY FINDINGS

Roentgen-ray examinations showed open epiphyses of all bones and fairly normal bone structure (fig. 3, table 1). The sella turcica was enlarged (fig. 4). During treatment, or at least since our first observations, the size of the sella turcica had diminished gradually from 23 by 19 mm. in 1936 to 19 by 13 mm. in 1942. Roentgen-ray examinations of the sella turcica were made by the same technic throughout. The diameter of the skull (20 cm.) did not change during observation, but the frontal and maxillary sinuses grew larger (frontal sinuses, 2 by 0.9 cm. to 3.5 by 1.8 cm.; maxillary sinuses, anteroposterior width 5 to 5.6 cm.). In 1942, the heart was not enlarged, the transverse diameter being 12 cm.; the transverse diameter of the chest was 31 cm.

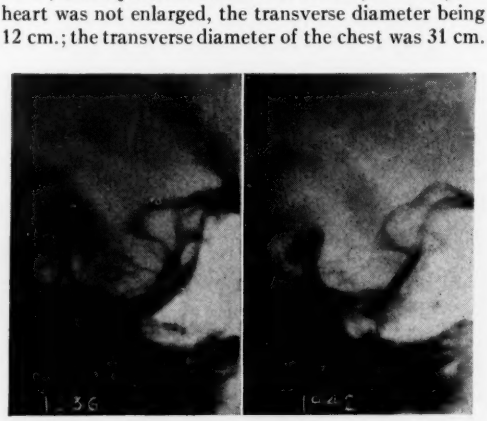

FIG. 4. REDUCTION OF SIZE IN SELLA TURCICA. Sella turcica of patient in 1936, *left*, and 1942, *right*. Approximate size; tube at 40 inches. Roentgenograms in between showed gradual decrease in size.

Tufting of the terminal phalanges did not increase much in spite of a great increase in the size of the hand.

TREATMENT

Roentgen-ray therapy. Evidence of intracranial pressure was lacking and the visual fields were normal, so that the question arose as to whether an attempt to prevent rapid growth in this patient should be made. He would in all probability grow rapidly and for a considerable length of time, in view of the January to July, 1936. On the other hand, the effect of roentgen-rays during the entire period of treatment might be questioned in view of the marked variation in height which the patient showed from time to time.

In spite of roentgen-ray therapy to the pituitary gland, each treatment consisting of 300 r, the patient grew 9 inches in the 5.5 years to the present time (fig. 2). During this time the size of the sella turcica decreased from 23 by 19 mm. in 1936 to 19 by 13 mm. in 1942.

TABLE 1. OBSERVATIONS OF BONE MATURATION

Dates of X-ray Observations	Terminal Phalanges	2nd Phalanges	3rd Phalanges	Metacarpal	Radial	Ulnar	Lower Femur	Upper Tibial	Estimated Bone Age[1]	Actual Age yr.
July, 1936	I	I	I	I	I	I	I	I	13	15
Mar., 1937										16
Dec., 1938										17
	Chorionic gonadotropin and pituitary gonadotropic injections started December, 1938									
Feb., 1939	I	I	I	I	I	I	I	I	13	18
May, 1939	II (thumb)	I	I	I	I	I	I	I	13 yr., 9 mo.	18
Sept., 1939	II	II	II	III	II	II	II	II	13.9	18
July, 1940	III–IV	II	II	III	III	III	III	III	15.3	19
Jan.. 1941	III–IV	III–IV	III	III	III	III	III	III	15.9	20
				Testosterone started January, 1941						
April, 1942[2]	V	V	V	IV	IV	IV	IV	IV	17.3	21

Key to grading of epiphyseal closure (approximate): I = wide open; II = early bridging but open; III = marked bridging; IV = closed with dense line; V = closed, dense line gone.

[1] Estimated on hand and wrist by standards from: Todd, T. W.: Altas of Skeletal Maturation, C. B. Mosby Company, 1937. While it is doubtful if bone age can be so nicely stated, it does provide a standard for comparison in one individual from year to year.

[2] Greatest increase in bone maturation appeared to have occurred between January, 1941 and April, 1942.

open epiphyses and the absence of secondary sex development. Consequently, roentgen-ray therapy was decided upon, hoping that by such means growth might be retarded and that at the same time pressure might be relieved from normal pituitary tissue, thus enabling gonadotropic principles to be liberated; these, in turn, would stimulate the development of secondary sex characteristics and epiphyseal closure. Cushing (15) suggested this explanation for sexual dysfunction in acromegaly. Roentgen-ray therapy was given intermittently from July, 1936, to December, 1941 (fig. 5). There appears to have been a leveling off of the rate of growth, particularly in view of the verified rate of growth in the previous 6 months from

Conadotropic and chorionic hormone therapy. In 1939, 3 years after the beginning of roentgen-ray therapy, no secondary sex characteristics had developed. It was felt that an attempt should be made to stimulate sexual development. Treatment was begun with pituitary gonadotropic hormone containing not less than 300 R.U. per cc. (sex maturity factor) and chorionic hormone of pregnant urine, containing 1000 R.U. per cc. Six days a week he was given 1.5 cc. of chorionic hormone and 0.5 cc. of pituitary gonadotropic hormone especially prepared by Collip.[1] These injections were begun on Dec. 5, 1938, and continued in a series

[1] Generously supplied by Ayerst McKenna and Harrison of Montreal.

of 4 treatments. A total of 300,000 R.U. of chorionic hormone and 30,000 R.U. of anterior pituitary gonadotropic hormone were administered during this time.[2]

Early in the course of the first series of injections the patient noted erections and occasional nocturnal emissions. There was definite increase in the size of the penis and testes by Feb. 1, 1939. The pubic hair had become rather long by the third course of treatment, but it was noted that there appeared to be slight regression in the size of the penis and an erection was poorly maintained.

During the fourth course of treatment there was no further enlargement of the penis and testes and in fact it was felt by his physician that there was some regression, suggesting that a possible antihormonal effect had been produced. There was also a definite lowering of the pitch of the voice and the appearance of slight facial lanugo. Treatment with anterior pituitary-like substance and gonadotropic hormone was therefore discontinued in December, 1939.

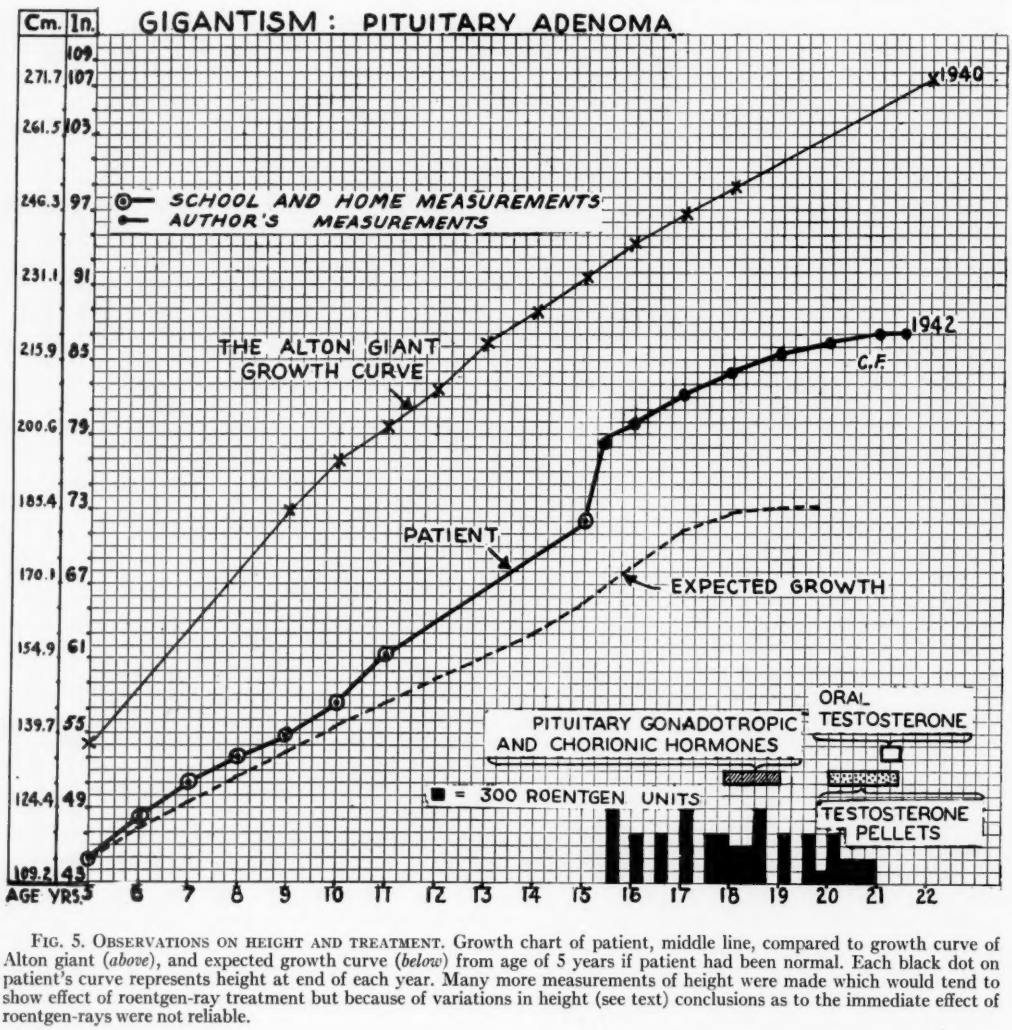

FIG. 5. OBSERVATIONS ON HEIGHT AND TREATMENT. Growth chart of patient, middle line, compared to growth curve of Alton giant (*above*), and expected growth curve (*below*) from age of 5 years if patient had been normal. Each black dot on patient's curve represents height at end of each year. Many more measurements of height were made which would tend to show effect of roentgen-ray treatment but because of variations in height (see text) conclusions as to the immediate effect of roentgen-rays were not reliable.

[2] These injections were given by Dr. J. Fletcher Wonson of Westfield, Massachusetts. The author is indebted to him for his coöperation and careful observations.

There was definite regression of the genital development, noted particularly in July and October of 1940. There was further regression of hair, and in December, 1940, as shown in figure 6, very little hair remained. There was some regression in the size of the testes and penis.

Testosterone therapy.[3] Pellets of testosterone were implanted subcutaneously in the thigh, as follows: 150 mg. Jan. 20, 1941; 150 mg. April 21, 300 mg. July 22; and 150 mg. Dec. 29.

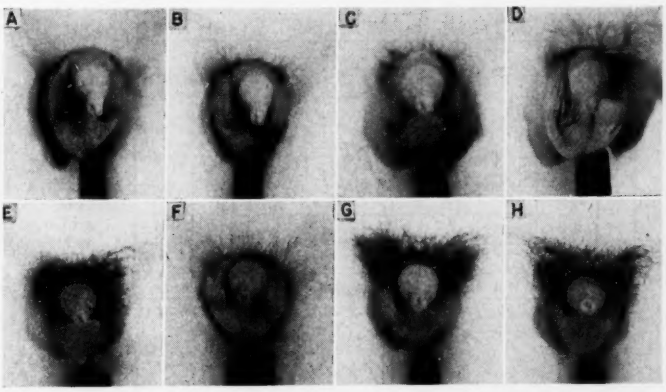

FIG. 6. GENITALIA, SHOWING DEVELOPMENT AND REGRESSION. A-E. (1/12/39 to 9/11/39) Development during gonadotropic and chorionic hormone therapy. F. (1/21/41) One year after discontinuing gonadotropic and chorionic hormone therapy; note regression. G. (7/21/41) Re-development after 6 months of testosterone pellet implantation (300 mg.). H. (4/27/42) Result 16 months after institution of testosterone therapy. There appears to be a slight regression owing to a decrease in therapy.

From Dec. 29, 1941, to April 27, 1942, testosterone in propylene glycol orally was taken at irregular intervals. On April 27, 1942, 150 mg. of testosterone was implanted.

Although development of secondary sex characteristics followed gonadotropic and chorionic hormone injections, a more satisfactory development followed administration of testosterone associated with a more marked deepening of the voice and more frequent erections. Judging from the latter indications of the effect of testosterone, 150 mg. appeared to be effective for as long as 4 to 6 weeks and 300 mg., about 6 to 8 weeks. More frequent and perhaps larger implantations would have been desirable. There appeared to be a more positive effect on epiphyseal closure and bone age during testosterone therapy (table 1) than during the gonadotropic and chorionic hormone therapy.

Neither type of hormone treatment appeared to stimulate growth. Evidence in the literature that testosterone has growth-promoting effects other than producing a possible prepuberal spurt is not convincing. The growth curve for this boy as well as the growth curves for hypogonadal individuals closely parallel normal growth curves. Evidence such as is demonstrated in cases of precocious puberty strongly points to the ability of the male sex hormone to close epiphyses at any age; in infancy or early childhood of such cases of otherwise normal individuals, limitation of longitudinal growth will and has taken place by virtue of epiphyseal closure.

Other therapy. During the 6 years of observation a sinus infection developed which was drained. Following this the patient had an infectious type of arthritis involving the feet and knees, with swelling and pain. This cleared up without any special treatment. He had difficulty with his feet and finally developed a very sore toe which was the result of a large exostosis under the big toenail. The patient had a secondary anemia of mild degree which was never benefited by iron. Following roentgen-ray therapy considerable lassitude developed which was markedly alleviated by the use of benzedrine, 5 mg. in the morning and at noon. When the apparent effect of the roentgen-ray therapy wore off, the patient always felt better. At only one time did he have 'shooting pains' in the head. This was only for a week or two at the most. Some dental caries appeared in October, 1940.

MEASUREMENT OF HEIGHT

The patient's mother discovered that the

[3] Testosterone pellets (Oretone F) and testosterone solution (Oretone F) in glycol were supplied by The Schering Corp., Bloomfield, N. J.

body length increased more than an inch after he had been lying in bed; this was verified when the patient went to the hospital for observation. In figure 7 is shown the variation in height during one week, and although the measurements were made by the boy's mother at home, it nevertheless illustrates how wide such differences may be. It is obvious that the patient is taller in the morning than when he goes to bed at night, and that he can vary his height considerably by standing straight and by deep inspiration. To obtain comparable results the height must, therefore, be measured at the same time of day, the best time being early in the morning when the patient has not been on his feet very long.

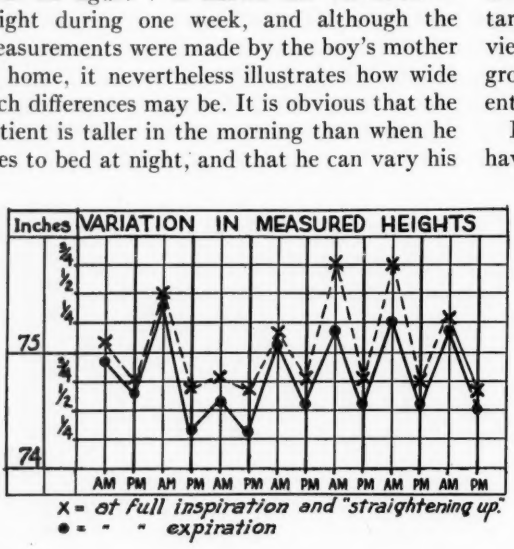

FIG. 7. VARIATIONS IN MEASURED HEIGHT. Observations were made by the patient's mother for 1 week, night and morning, after full inspiration and 'straightening up.' These results illustrate the necessity for making measurements under uniform conditions. A rigid apparatus should be used, or if not available, some solid object with right angles, such as a book, should be held firmly against the wall and on top of the patient's head.

Roentgen-ray treatments were often given on the basis of change of height from one visit to another, but these changes were not necessarily an indication of growth.

DISCUSSION

There is no evidence in this case of excessive secretion of pituitary hormones other than the growth factor. Certainly, there has been a deficiency of gonadotropic factor or factors. Since there was a low basal metabolic rate and neither enlargement of the thyroid nor clinical signs of hyperthyroidism, there can be no increase of the thyrotropic principle. The low values for the sugar curve eliminate the possibility of diabetogenic effect. The normal water test for adrenal insufficiency demonstrates no marked reduction in adrenotropic principle such as is frequently found in patients with chromophobe tumors. Anemia is commonly found in the latter type of case. Thus one is justified in believing that this patient has an acidophilic adenoma producing an excessive amount of growth factor with suggestive evidence of deficiency of some of the other pituitary hormones. From a clinician's point of view, this case supports the view that the growth factor may well be a distinct hormonal entity.

In reviewing our experience with this case we have concluded that in future attempts to limit growth in such cases, we would give roentgen-ray therapy for a few months in the hope that genital development might take place, and if so, the roentgen-ray therapy would be maintained as long as such continued. If no such development resulted within 3 to 6 months, then surgical removal of the adenoma would be advised. If this procedure were not followed within a few months by genital development, testosterone therapy would be instituted at once. If surgery were refused, both roentgen-ray therapy and testosterone should be given. If when first seen the patient's growth had reached a height which, with a few more inches of growth, would burden him with all of the difficulties which beset a real giant, surgical removal of the tumor would be justified as soon as possible.

CONCLUSION

A case of pituitary gigantism is presented. Stimulation of genital development occurred with combined pituitary gonadotropic and chorionic hormone injections; regression followed its discontinuance. Thereafter testosterone implantations produced genital development and epiphyseal closure, thus arresting

longitudinal growth. Roentgen-ray therapy appeared to have been effective in retarding growth when it was first used. Early operation is urged in these cases if other measures fail to promise cessation of growth.

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The Use of Adrenal Extract in Fever Therapy[1]

A. Edelmann, D. L. Mahanna, L. A. Lewis, J. S. Thatcher and F. A. Hartman

From the Departments of Physiology and Medicine, Ohio State University, Columbus, Ohio

It had been observed by one of us (D.L.M.) that adrenal extract alleviated many of the ill effects of fever therapy. Weakness, nausea and vomiting were reduced. Herpes was absent or less severe. Recovery was more rapid and subsequent treatments were tolerated better. The present study is an attempt to discover the underlying factors involved in this effect.

The copious perspiration from fever therapy reduces the sodium chloride in the body. If the sodium depletion becomes marked, weakness and nausea may develop (1). Adrenal extract can cause sodium retention by the kidney in normal human beings (2). It might reduce the excretion of sodium through the skin and thus ameliorate the symptoms resulting from fever therapy insofar as they were due to sodium depletion. We have investigated the effect of adrenal extract on the electrolyte metabolism of patients treated by fever therapy.

METHODS

The patients were treated by the Kettering Hypertherm. The patient, with the exception of his head, was surrounded by circulating hot air. Humidity and temperature were high (90–95%; 125–130°F.) initially, until the desired fever level was reached and then lowered to 30–35% and 115–120°, to maintain the elevation of body temperature.

Body temperature (rectal) was raised to 105–106° F. The period of induction was 30 to 45 minutes. The patient was maintained at fever temperature for 2 hours and 45 minutes unless complications arose. The temperature was controlled by means of a thermostat connected with a thermocouple inserted into the rectum.

The subjects were patients at the University Hospital, suffering from syphilis of the central nervous system. They were all comparable as far as could be determined by electrocardiograph, physical examination and blood chemistry.

Treatments were given once a week. In the first series there were no dietary restrictions except that the patient was requested to salt his food as much as possible and to drink fruit juices between treatments. Each patient was hospitalized for 24 hours following treatment.

In the second series the patients were hospitalized for the entire period of treatment (12 weeks) in order to control diet and activity.

Blood was drawn from the basilic vein just before the patient entered the cabinet and again at the end of the treatment before the body temperature dropped.

In the first series 6 cc. of extract was injected intramuscularly immediately after withdrawal of the first blood sample, and 4 cc. was injected following removal of the patient from the cabinet. In the second series, the second injection of 4 cc. was given when the peak of fever level was reached. Desoxycorticosterone acetate was in-

Received for publication July 23, 1942.

[1] Aided by grants from The National Research Council Committee on Research in Endocrinology and The Comly Fund of The Ohio State University.

jected in oil. Placebos were injected during control periods. Each patient received 1/64 grain of dilaudid and 1/400 grain of scopolamine just prior to treatment. These injections were repeated when the desired fever temperature had been attained.

The patient was required to drink 1500 cc. of distilled water during treatment. After withdrawal of the second blood sample, water was permitted *ad libitum*. No sodium chloride was administered on the day of treatment until after the second blood sample was taken.

In the second series with the controlled diet, all food was purchased in one consignment for the whole experiment in order to insure constancy of composition. Patients received the same amount of food and water daily and 4 grams of salt was added; the water was distilled. The subjects were considered to be in balance when the urine volume and the chloride excretions were constant for 3 successive days. Experiments were then begun. Chloride excretion was determined at random intervals to ascertain the maintenance of balance.

The excretion of electrolytes in the perspiration was determined by the collection of sweat in clean rubber gloves held at the wrist by rubber bands. The hands were washed at the beginning and at the end of the period with distilled water.

Sodium was determined by the method of Butler and Tuthill (3), potassium by Consolazio and Talbott's modification of Shohl and Bennett's method (4), chloride by the modified Volhard-Harvey titration method (5). The volume per cent of packed erythrocytes was determined by the method of Wintrobe (6). Hemoglobin was determined by the Haden-Hauser hemoglobinometer, and total protein by the Pregl modification of the micro-Kjeldahl method (7). Proteins were fractionated by the method of Campbell and Hanna (8). Clotting was prevented by heparin except in the portion of blood used for fibrinogen determinations. Potassium oxalate was employed in the latter. Sugar was determined by the method of Benedict (9).

An attempt has been made to show the response of the patient to extract by appraising the effect on fatigue and on the time of recovery. Four degrees of fatigue and recovery have been employed in each instance as follows:

FATIGUE

Degree	
1	Little or no weakness
2	Moderate weakness
3	Marked weakness. Moves with difficulty
4	Complete exhaustion. Movement impossible

RECOVERY

Degree	
1	Within 12 hours
2	12 to 36 hours
3	36 to 72 hours
4	More than 72 hours required

Recovery was indicated by the absence of nausea and vomiting, ability to retain food, absence of headache, and a state of well being. Two or more of the authors made these classifications independently. One of them was uninformed as to the administration of extract.

RESULTS

Twelve patients were studied in this investigation, each one for a period of 10 weeks.

It appeared that adrenal extract prevents or reduces the fall in plasma sodium in some instances, has no effect on plasma potassium and may or may not affect the plasma chloride. It appeared to have a very decided effect in reducing the degree of fatigue and rate of recovery after one or two treatments (table 1).

TABLE 1. EFFECT OF ADRENAL EXTRACT ON REACTIONS TO FEVER THERAPY

RECORD OF A TYPICAL PATIENT (*J. M.*)

Plasma electrolyte changes in milliequivalents per liter

Treatment, No.	Extract cc.	Na	K	Cl	Reaction	
					Fatigue	Recovery
1	0	−2.1	−0.8	−3.6	2	3
2	0	−3.7	+0.1	+1.0	2	4
3	0	−5.6	+0.5	−1.0	3	4
4	0	−9.0	0.0	−0.8	3	4
5	0	−5.2	−1.5	+2.0	3	4
6	10	+0.7	−1.1	+5.0	2	4
7	10	+0.2	−0.1	−4.6	2	2
8	10	−0.6	−0.4	+7.2	1	1
9	10	−2.0	+0.6	+4.8	1	1
10	10	−1.7	+1.6	−1.6	1	1

It will be noted that the reaction to the first treatment without extract is better than succeeding ones. When extract was used there was slight improvement at first. With successive in-

TABLE 2. EFFECT OF ADRENAL EXTRACT ON REACTIONS TO FEVER THERAPY

Patient	Sodium[1]		Potassium		Chloride		Reaction			
							Fatigue		Recovery	
	Without	With	Without	With	Without	With	Without	With	Without	With
J.M.	−5.0	−0.8	−0.3	−0.6	−0.5	+2.0	2.6	1.2	3.8	1.8
V.W.	−1.8	+0.2	+0.3	+0.2	−1.3	+2.2	2.5	1.2	3.6	2.0
W.W.	−3.9	+2.6	−0.5	−0.1	0	+3.7	4.0	1.0	3.6	2.0
C.A.	−2.7	+0.3	−0.3		−0.7		3.4	1.2	3.8	1.8
W.T.	+0.5	−0.2	−0.1	0	0	−5.5	2.2	1.0	3.4	1.2
M.M.[2]	−2.4	+0.6	+0.2	+0.1	−1.8	+5.7	2.5	1.0	4.0	1.4
G.W.	−0.1	−3.2	+0.1	+0.2	−0.7	−7.2	3.0	1.6	3.6	1.6
C.M.[2]	+3.2	+0.6	+0.2	+0.2	−0.8	+2.9	1.8	1.0	3.2	1.0
L.H.[2]	−1.5	+0.1	+0.4	+0.4	−0.3	+3.0	3.3	1.0	3.6	1.3
R.M.[2]	−1.8	−1.1	+0.5	+0.7	−0.7	−2.5	2.5	1.4	3.5	1.8

[1] Plasma electrolyte changes in milliequivalents per liter. Each value is the average of 5 treatments.
[2] Signifies treatments with and without extract were alternated; in all others, five treatments with extract followed five treatments without extract.

jections this improvement became quite marked. The first 5 periods of treatment serve as control periods for the last 5, when extract was used.

If one averages the results of 5 treatments with extract and the 5 treatments without extract in each patient he can see that the reaction is improved with extract. This is true whether the extract is used in consecutive treatments or in alternate treatments (table 2).

A better picture of the changes which occur with successive treatments is given in figure 1 in which each point is obtained by averaging the values from 6 patients. It will be noted that

In order to determine the effect of increased dosage 10 cc. of extract, instead of 6 cc., was administered prior to fever therapy in one treatment for each of 3 patients. There was a definite increase in sodium retention. The increases were 4.6, 6.7 and 8.2 m.eq./liter, respectively. There was no increase in the effect on fatigue and recovery.

There was considerable variation in the plasma electrolytes at different tests; therefore, determinations were made in 2 patients whose diet was controlled in the hospital, as mentioned above, in order to rule out this factor. Tables 3 and 4 contain the results. There was

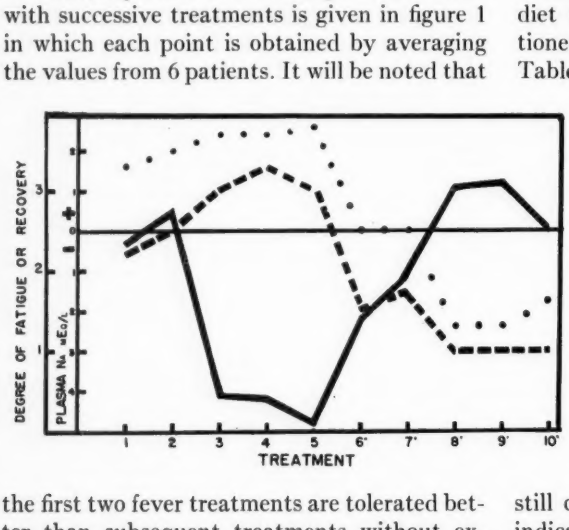

FIG. 1. EFFECT OF ADRENAL EXTRACT ON FATIGUE, RECOVERY AND PLASMA SODIUM change which follow fever therapy treatments. Each point is the average of values from 6 patients. *Adrenal extract injected. *Solid line*, sodium; *broken line*, fatigue; *dotted line*, recovery.

the first two fever treatments are tolerated better than subsequent treatments without extract, while the plasma sodium shows little or no change. Although the extract favorably affects fatigue and recovery the first time it is used, the effect is greater in the treatments that follow.

still considerable variation in the response as indicated by the sodium retention. It will be noted that there was a significant loss of plasma sodium during the third treatment in *patient R. M.* (table 3). This is explained by an accident which occurred. During treatment a short circuit developed in the thermostat so that the

rectal temperature rose to 107.4° F. It was 50 minutes before this was reduced to normal level. The subject was irrational and comatose in turn and did not fully recover from the effects until 36 hours later. It is the belief of the staff of the fever therapy division that the use of extract prevented more serious consequences, judging from their experience in similar incidents in which extract was not used.

Because the patients were hospitalized a more thorough study of the reactions could be made in *R. M.* and *L. H.* Detailed accounts of their reactions are therefore given.

Patient R. M. The first treatment resulted in a feeling of weakness which persisted for several hours after the return of body temperature to normal. This might be expected in a patient undergoing fever therapy for the first time. The attendant fear and anxiety produced considerable emotional stress. Repetition tended to remove these factors. With the exception of the third treatment, noted above, the patient was not nauseated nor did he vomit during any treatment in which adrenal extract was given. He was nauseated and vomited twice when no extract was given (treatments 8 and 10), the latter when desoxycorticosterone was given. He appeared exhausted following treatments without extract. He was unable to stand on the scales. He slept longer. With extract he was not only able to stand unassisted but walked to the scales. The relation between the change in plasma sodium and fatigue and recovery is shown in figure 2. The low value of plasma sodium at the third treatment is a result of the large loss of sodium due to the accidental overheating mentioned above. With the exception of this third period in the one subject, retention of sodium accompanied amelioration of the fatigue.

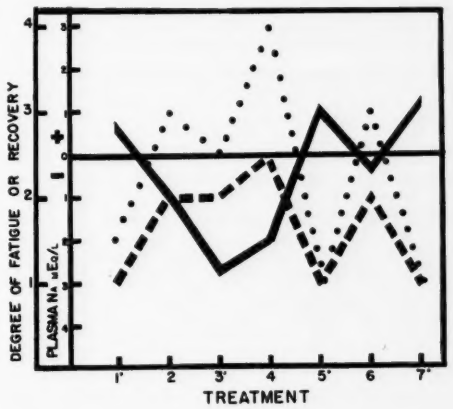

FIG. 2. EFFECT OF ADRENAL EXTRACT ON FATIGUE, RECOVERY AND PLASMA SODIUM change which follow fever therapy. Legend is the same as in figure 1 except that adrenal extract was injected at alternate treatments. Each point is the average of values from two patients.

Patient L. H. (table 4). This patient was more severely affected by fever therapy than was *R. M.* Nausea and vomiting did not appear until the third treatment, although weakness was evidenced from the first. The treatments without extract were always marked

TABLE 3. EFFECT OF ADRENAL EXTRACT ON REACTIONS TO FEVER THERAPY

Treatment Number	Extract, cc.	Sodium[1]		Potassium		Chloride		Blood sugar, mg. %		Reaction	
		Pre-fever	Post-fever	Pre-fever	Post-fever	Pre-fever	Post-fever	Pre-fever	Post-fever	Fatigue	Recovery
Patient R.M.											
1	10	140.3	139.5	4.4	7.2	105.3	104.2			1	2
2	0	139.8	138.5	5.2	6.5	106.2	103.8			2	3
3	10	138.9	135.4	5.4	6.6	104.4	102.2			3	4
4	0	139.0	130.9	5.5	6.6	104.7	103.4			3	4
5	10	142.0	141.5	4.9	4.8	103.8	101.5	87	95	1	1
6	0	142.3	138.2	5.6	5.4	93.8	94.8	123	108	2	3
7	10	138.9	140.0	4.9	5.1	95.0	91.8	97	103	1	1
8	0	140.2	138.3	5.0	5.0	103.1	104.7	120	90	3	4
9	10	141.8	144.2	5.1	4.5	99.2	96.2	107	110	1	1
10	1.5 mg.[2]	140.0	142.5	5.1	5.7	100.2	99.4	105	123	3	4

[1] Plasma electrolyte changes in milliequivalents per liter.
[2] Desoxycorticosterone acetate.

by the almost complete lack of strength. He was unable, on such occasions, to raise his body in order to rinse his hands in water. Indeed, on two occasions it was a real effort for him to raise his arms. When extract was administered, he was able to sit up of his own accord. He experienced nausea and vomiting when extract was not given. Administration of extract did not completely remove these symptoms, but their frequency and intensity were diminished.

tract had been administered during the first series. It had been found necessary to decrease the length of time he was maintained at fever level after the fifth treatment because of increasing nausea, vomiting and weakness. This was unnecessary in the second series when extract was given.

Patient F. H. received a series of treatments in 1937. After the fifth session, nausea was so acute as to prevent her taking fluids. Weakness increased in degree

TABLE 4. BLOOD AND PERSPIRATION CHANGES IN A PATIENT (*L. H.*) WITH AND WITHOUT ADRENAL EXTRACT DURING FEVER THERAPY

Treatment No.	Wt. Loss kg.	Hb. gm.%	Erythrocytes vol. %	Plasma						Blood Sugar, mg. %	Electrolyte Excretion[3] in Perspiration m.eq.			Reaction	
				Electrolytes			Proteins								
				Na m.eq. per liter	K m.eq. per liter	Cl m.eq. per liter	Total gm. %	Albumen gm. %	Globulin gm. %		Na	K	Cl	Fatigue	Recovery
1		14	51	140.0	5.8	102.6	6.96	4.54	2.42						
	2.07	14.5	52.5	138.1	5.9	102.2	7.18	4.70	2.48		237.9	13.1	115.3	3	4
2[1]		14	49	138.3	5.5	101.2	6.65	4.70	1.95						
	3.20	15		140.8	5.6	105.6	7.40	4.98	2.42		200.7	10.5	87.6	1	2
3		15	50	138.5	4.7	95.4	6.66	4.60	1.06	109					
	3.17	16	52	135.0	5.3	99.0	6.80	4.86	1.94	98	332.0	12.4	111.0	4	4
4[1]		13	51	139.0	4.6	101.8	6.56	4.60	1.96	84					
	3.17	15	54	137.2	5.4	101.8	6.65	4.92	1.73	94	285.3	13.7	92.8	1	1
5		14	54	134.9	5.5	89.2				124					
	3.20	15	55	136.0		92.6				84	340.5	22.5	155.1	2	3
6[1]		14	49.5	137.8	4.8	100.0	6.30	4.09	2.21	122					
	3.14	15	51	139.8	5.1	105.0	7.00	4.25	2.75	127	195.8	8.5	70.8	1	1
7		14	51	137.5	4.8	109.4	6.82	4.58	2.24						
	3.52	15	53	135.5	5.4	101.8	7.17	4.82	2.35	93	303.4	27.8	95.0	4	4
8[2]		14	51	138.3	5.5	99.8	6.65	4.58	2.07	95					
	3.06	15	54	140.2	6.2	104.4	6.90	5.12	1.78	101	300.9	22.5	81.2	4	4

[1] 10 cc. extract.
[2] 1.5 mg. desoxycorticosterone acetate.
[3] Calculated from concentration and 80 per cent of weight loss.
Roman type, before, bold-faced type, after fever therapy.

A study of the case records of patients treated by fever therapy without extract under the supervision of one of the authors (D. L. M.) previous to this study has shown that 80 per cent of the cases could stand no more than 4 or 5 treatments similar to those employed in this investigation. The debility, nausea and general malaise were so great that fever had to be discontinued or the duration of fever shortened. Lengthening of the interval between treatments was sometimes employed. A few examples will suffice.

Patient M. M. took a series of treatments in 1939, and a year later was one of the experimental subjects while undergoing therapy for the second time. No ex-

with each treatment and the duration of treatment had to be diminished.

Other incidents are of importance. Several patients had to be removed from the cabinet because of malaise and nausea. In three instances this occurred even though the treatment time had been shortened. Patients reported having to remain in bed for 2 to 4 days following treatment, thus losing valuable work time.

Since the use of extract in conjunction with fever therapy has been instituted, no patient, even subjects who had no extract during the first 5 treatments, has had to be removed from the cabinet because of these symptoms, nor has

any patient had to have the later treatments shortened or postponed. The majority of patients have been able to leave the hospital the day of treatment.

The hemoglobin and volume per cent of packed erythrocytes were determined in all subjects. The results from a typical case are shown in table 4. The increase in both values figure in our table in calculating the total electrolyte loss.

It will be seen that the total sodium excreted in sweat was reduced in both patients when extract was given, except in the first and ninth treatments of *patient R. M.* There was reduction in the total potassium excreted in some instances when extract was given. The results

TABLE 5. INFLUENCE OF ADRENAL EXTRACT ON ELECTROLYTE EXCRETION IN SWEAT

Patient and Treatment No.	Extract, cc.	Perspiration gm.	Sodium		Potassium		Chloride	
			Concentration m.eq. per liter	Total[1] m.eq.	Concentration m.eq. per liter	Total m.eq.	Concentration m.eq. per liter	Total m.eq.
R.M.								
1	10	2056	89.0	183.0	6.1	12.5	39.2	80.6
2	0	2125	84.5	179.6	6.5	13.8	30.4	64.6
3	10	*	83.3		6.5		29.6	
4	0	3571	105.1	375.3	5.6	20.0	42.4	151.4
5	10	1693	84.0	142.2	5.4	9.1	34.2	57.9
6	0	1997	123.0	245.6	6.1	12.2	56.2	112.2
7	10	1852	117.0	216.7	5.2	9.6	37.2	68.9
8	0	2400						
9	10	1852	128.0	237.1	7.9	14.6	73.8	136.7
10	1.5 mg.[2]	*	132.0		10.3		78.8	
L. H.								
1	0	1657	143.6	237.9	7.9	13.1	69.6	115.3
2	10	2563	78.3	200.7	4.1	10.5	34.2	87.6
3	0	2534	131.0	332.0	4.9	12.4	43.8	111.0
4	10	2536	112.5	285.3	5.4	13.7	36.6	92.8
5	0	2560	133.0	340.5	8.8	22.5	60.6	155.1
6	10	2510	78.0	195.8	3.4	8.5	28.2	70.8
7	0	2812	107.9	303.4	9.9	27.8	33.8	95.0
8	1.5 mg.[2]	2446	123.0	300.9	9.2	22.5	33.2	81.2

* Too weak to be weighed.
[1] Milliequivalents excreted calculated from concentration and perspiration.
[2] Desoxycorticosterone acetate.

reflected the hemoconcentration. This effect did not appear to be modified by adrenal extract.

Blood sugar. The blood sugar was determined in *patients R. M.* and *L. H.* It fell in every instance when extract was not administered. When either extract or desoxycorticosterone was given the blood sugar rose somewhat (tables 3 and 4).

Secretion of electrolytes in sweat. The electrolyte content of sweat was studied in the two hospitalized patients. The results are shown in tables 4 and 5. Extract caused reduction in the concentration of sodium in the sweat in all instances, in both patients except the first and ninth treatments of *patient R. M.*

The water loss through sweating was estimated as 80 per cent of the total weight loss (see discussion). Therefore we have used this with total chloride were similar to those with total sodium.

Plasma proteins were determined in both patients. The results in one only are shown because they are similar to those in the others. There were no significant variations in total protein, albumin, globulin and fibrinogen (table 4). The last is not shown in the table.

DISCUSSION

A course of treatments given to a patient not fortified with extract results in a progressive decline in the ability to withstand the rigors of hyperthermia. Debility, nausea, vomiting and recovery time tend to increase with the number of treatments. There is apparently some injury to the heat-resisting centers, for patients taking a second series of treatments exhibit these symptoms to a far greater degree than they

were previously demonstrated although the earlier series was taken 3 or 4 years previous to the later course. Our results indicate that adrenal extract may protect the centers involved from this damaging effect of the hyperthermia.

Herpes usually occurs following the first and sometimes the second treatments. It may be said that, in general, it does not occur in the later treatments. As the majority of our patients did not receive extract until the sixth treatment we were unable to observe the effect of adrenal extract upon the incidence of this condition.

Maddaloni (10) found in rabbits that adrenal extract increased the resistance to heat.

Our assumption that 80 per cent of the weight loss was due to water lost in the perspiration is based on the work of Dill (11). He determined the weight loss in a human being who walked 6.8 km. per hour for 2.5 hours at a shade temperature of 33° C. and a humidity of 11 per cent. The weight lost as carbon dioxide and water through the lungs and water in insensible perspiration was about 20 per cent, leaving a balance of 80 per cent for perspiration.

Because adrenal extract often prevents or reduces the fall in plasma sodium, when fatigue and other symptoms are diminished, one might conclude that sodium retention was responsible for the amelioration. However, there were instances in which marked amelioration of symptoms occurred without retention of sodium. Therefore, if sodium retention contributed to the effect it was not the essential factor in the improvement. Moreover, these changes appeared to be too small to be effective.

It was impractical to determine plasma volume during fever therapy. It can only be estimated from the volume of packed erythrocytes. If this is done, it is found that the increase in sodium concentration is not explained by loss of water from the plasma.

Honaga (12) found that fever produced by most infections in man, or experimentally induced in rabbits, increased the plasma potassium. Our results did not agree with his, perhaps because of the relatively short exposure and difference in source of pyrexia.

The results obtained in the study of electrolyte excretion in sweat indicate actual retention of sodium when extract was used. The actual change in plasma sodium as well as that calculated on the basis of total excretion was not marked. This is evidence that sodium retention cannot be an important factor in the amelioration of the unfavorable reactions to fever therapy.

It is impossible to account for the wide variation in 'basal' blood sugar values. This variation may have been due to different degrees of excitement preceding treatment. In our experiments there was a rise in blood sugar during fever therapy with extract, although it was sometimes small. This was in contrast to the fall which occurred when extract was omitted. The latter finding is in contrast to the results of Loseke and Gunderson (13) who obtained a rise in blood sugar during artificial fever in rabbits. Our subjects were in the post-absorptive state for 21 hours having been without food for 15 hours before the experiment, in addition to 6 hours of fever. Fever is effective in depleting the liver glycogen (13), while adrenal extract promotes gluconeogenesis (14). These results might possibly be due to gluconeogenesis or decreased sugar utilization or both.

It is noteworthy that extract administered in earlier treatments exerted an influence upon later treatments, even if extract was not given. Some of the symptoms produced by fever involve the central nervous system. Their amelioration by extract may be due at least in part to an effect on this system. It has been observed before that the effect of adrenal extract on the central nervous system may persist for more than 3 weeks after its administration (15).

Hyperthermia impairs the oxygen-carrying capacity of the blood (16). Moreover, Himwich *et al.* (17) believe that the cerebral circulation is reduced, yet the metabolism is increased. The oxygen uptake by brain tissue may be further impaired by reduction in efficiency of the enzyme systems at the high temperature. Hitchcock *et al.* (18) have shown that in mild exercise adrenal extract causes a decrease in oxygen consumption in normal human beings. Tipton corroborated this for liver and brain slices (19). Thus the effect of adrenal extract on the nervous system might be explained by the decreased demand for oxygen.

SUMMARY

The effect of adrenal extract on 12 patients treated by fever therapy weekly for 10 weeks was studied. This extract decidedly reduced the degree of fatigue and accelerated the rate of recovery after one or two treatments. The frequency and intensity of the other symptoms were also favorably affected. Desoxycorticosterone acetate produced no beneficial effect.

Extract prevented or reduced the fall in plasma sodium in many instances but had little effect on the potassium, chloride and proteins. This was explained by the reduction in excretion of sodium in the perspiration. Potassium and chloride excretion in the perspiration was reduced also in some instances. The retention of sodium when adrenal extract was given was insufficient to account for the amelioration of the unfavorable clinical reactions to fever therapy.

Blood sugar fell when extract was not given but rose when it was administered.

It is suggested that extract may act upon the central nervous system.

We are indebted to Dr. C. A. Doan for the use of the facilities at the University Hospital. We also wish to thank Miss Lucille Kester for her assistance in the treatment of the patients and Miss Emma McCormick for supervision of the diet.

Dr. E. L. Green gave valuable aid in arranging the data. The adrenal extract was furnished by Dr. G. F. Cartland of The Upjohn Co., Kalamazoo, Mich. The desoxycorticosterone acetate was supplied by Dr. R. D Shaner of Roche-Organon, Inc., Nutley, N. J.

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Diabetes Mellitus without Other Endocrine Manifestations in a Case of Tumor of the Adrenal Cortex

RANDALL G. SPRAGUE, M.D.,
JAMES T. PRIESTLEY, M.D. AND
MALCOLM B. DOCKERTY, M.D.

From the Divisions of Medicine, Surgery and Surgical Pathology, Mayo Clinic, Rochester, Minnesota

IN THE LIGHT of present-day knowledge of the rôle of the adrenal cortex in carbohydrate metabolism, it is not surprising that there is more than an accidental incidence of frank diabetes or minor disturbances of carbohydrate metabolism in cases of tumor of the adrenal cortex in man. Almost always if there is an impairment of carbohydrate metabolism it is but one, and usually a minor, manifestation of hyperfunction of the adrenal cortex. Rarely amenorrhea is the only endocrine manifestation and occasionally a tumor evidences itself only as an abdominal mass, but as a rule, there are multiple sexual and somatic abnormalities such as hirsutism, genital changes, girdle obesity, striae, acne, polycythemia and osteoporosis. Indeed these are usually more prominent features than are perversions of carbohydrate metabolism.

In 1939, Shepardson and Shapiro reviewed the literature and were able to find 17 cases of tumor of the adrenal cortex associated with diabetes in which the diagnosis was acceptable to them, and added one of their own. In all of these there were other endocrine signs in addition to diabetes. In fact, a review of all cases of tumor of the adrenal cortex reported in the literature does not reveal any instance in which diabetes has been the sole endocrine manifestation.

The case to be reported is one in which a disturbance of carbohydrate metabolism having the characteristics of frank diabetes mellitus was the only endocrine disturbance associated with a malignant tumor of the adrenal cortex. It is of particular interest because of its bearing on current philosophy concerning the multiplicity of functions and secretions of the adrenal cortex.

Received for publication October 28, 1942.

CASE REPORT

The patient, a woman, aged 49 years, was referred to the Mayo Clinic in February 1941. Her chief complaint was of diarrhea which had come on gradually 6 weeks previously. Giardia lamblia had been found in the stools, and the infestation had been treated with atabrine dihydrochloride. A large mass in the right upper quadrant of the abdomen had also been noted at that time. Glycosuria had been discovered 3 years previously when the patient had consulted a physician because of generalized pruritus. At that time she weighed 147 pounds (66.7 kg.). There was no history of diabetes in other members of her family. Immediately following the discovery of glycosuria she had started using small doses of protamine zinc insulin. Control of glycosuria proved to be difficult, and within a year the dose had been increased to 125 U of protamine zinc insulin daily, and subsequently to a total combined dose of unmodified and protamine zinc insulin of 145 U daily. In spite of the large doses of insulin, there had been no hypoglycemic reactions. As

far as could be determined, there had been no episodes of ketosis. The blood sugar during fasting two weeks before the patient came to the clinic had been 375 mg. per 100 cc., and a week later it had been 250 mg. per 100 cc. Since that time she had been eating a diet containing 146 gm. of carbohydrate and had been taking 30 U of protamine zinc insulin and 15 U of unmodified insulin daily, injected in one syringe in the morning before breakfast. Glycosuria had been irregularly controlled.

The essential findings of the physical examination were mild hypertension, the blood pressure being 160 mm. Hg systolic and 94 diastolic, and a large, deep, movable mass in the right upper quadrant of the abdomen which did not seem definitely attached to the liver. Examination of the ocular fundi revealed slight narrowing and sclerosis of the retinal arteries. There was some choroidal degeneration suggestive of old focal choroiditis in the regions of both maculae. The patient's weight was 114 pounds (51.7 kg.). The habitus was normal, the amount and distribution of body hair were normal, and except for atrophic changes of the vulva and vagina, there were no abnormalities of the external genitalia or pelvic organs. The menstrual history was normal, and she was still menstruating regularly. Values for hemoglobin, erythrocyte count, leukocyte count and differential count were normal. Several urinalyses revealed, in addition to glucose, varying amounts of albumin and from 8 to 40 pus cells per high-powered field. A flocculation test for syphilis gave negative results. The fasting blood sugar was 252 mg. per 100 cc. The values for blood urea, serum bilirubin, serum amylase and serum lipase were all normal. The bromsulfalein test of liver function did not show any retention of dye after one hour. Roentgenologic studies showed the abdominal mass to be extrinsic to the stomach and duodenum, the colon, and the right kidney and ureter. These structures all appeared normal except for displacement to the left by the mass. The gallbladder did not visualize on cholecystography. There was no free hydrochloric acid in the gastric contents after a test meal. There was no excess fat in the stools.

Without a definite diagnosis of the nature of the abdominal mass, surgical exploration was decided upon. During the period of study before operation, the patient was given a combined dose of unmodified and protamine zinc insulin each morning totaling between 30 and 68 U, the smaller doses being administered on days when meals were omitted because of roentgenologic studies. The diet contained 147 gm. of carbohydrate, except for the 4 days preceding exploration of the abdomen, when the carbohydrate content was increased to 254 gm. As much as 28.7 gm. of glucose was excreted in the urine in 24 hours while the patient was eating the former diet. Ketone bodies were never found in the urine. There were no hypoglycemic reactions.

Operation. Exploration of the abdomen was performed through a right rectus incision on March 12, 1941. There was a mass about the size of a football situated retroperitoneally behind the right lobe of the liver and above the kidney. The gallbladder was large and somewhat distended, and it was felt that it failed to visualize on cholecystography because of extraductal pressure. Exploration of the stomach, duodenum and pancreas gave negative results, although all of these structures were pushed over to the left by the tumor mass. Following incision of the peritoneum lateral to the ascending portion of the colon a fairly good line of cleavage was found around the tumor and accordingly it was mobilized and removed. As far as could be determined, it was not connected with any adjacent organ and was completely removed. A transfusion of 1000 cc. of citrated whole blood was given.

The value of the blood sugar one hour after the operation was 303 mg., and 4 hours later it was 210 mg. per 100 cc. On the third postoperative day it was 107 mg., and on the fifth postoperative day it was 88 mg. per 100 cc. The urine remained consistently sugar-free following the day of the operation. The dose of insulin was gradually reduced, and it was finally discontinued on the sixteenth postoperative day. In retrospect it seemed that it might have been discontinued much earlier than it was. No signs or symptoms of adrenal cortical insufficiency developed in the early postoperative period except for a fall of blood pressure to a low value of 80 mm. Hg systolic and 60 diastolic 6 hours after the operation. No adrenal cortical therapy was administered.

Subsequent investigations of the patient's carbohydrate metabolism all gave normal results. On the twenty-fifth postoperative day an oral glucose tolerance test of the Exton and Rose (2) type was performed with the following result.

Time, min.	Glucose Given, gm.	Blood Sugar, mg.	Urine Sugar
0	50	85	0
30	50	122	
60		144	0

Eight months after removal of the tumor, the patient was reexamined. There was no evidence of recurrence of the tumor. The blood pressure was 166 mm. Hg systolic and 102 diastolic, and she was in good general condition. She had not menstruated in 6 months and she was experiencing occasional hot flushes. An oral glucose tolerance test of the Exton and Rose type gave the following result:

Time, min.	Glucose Given, gm.	Blood Sugar, mg.	Urine Sugar
0	50	88	0
30	50	142	
60		175	0

At this time a standard 3-hour oral glucose tolerance test gave the following result:

Time, min.	Glucose Given, gm.	Blood Sugar, mg.	Urine Sugar
0	57	76	0
30		152	0
120		70	0
180		74	0

Eighteen months after removal of the tumor the patient reported by letter that she was in good health,

that the urine had remained free of sugar and that a recent determination of the blood sugar had been normal. The original diarrhea, which had subsided soon after the operation, had not recurred.

Pathologic data. Grossly the tumor measured approximately 20 cm. in diameter and weighed 1550 gm. The outer surface was coarsely lobulated and invested with a thin but fairly complete capsule in which no remnant of the suprarenal gland could be identified (fig. 1).

Surfaces made by cutting revealed a soft, friable, light yellowish tissue interspersed here and there with dark red zones of hemorrhage and white patches of necrosis. Flimsy bands of fibrous tissue coursing in from the capsule subdivided the tumor into large, irregular lobules but apart from these regions the neoplasm seemed grossly to be almost devoid of stroma. A few large veins could be seen in and near the capsule. These veins were apparently free from tumor 'thrombi.'

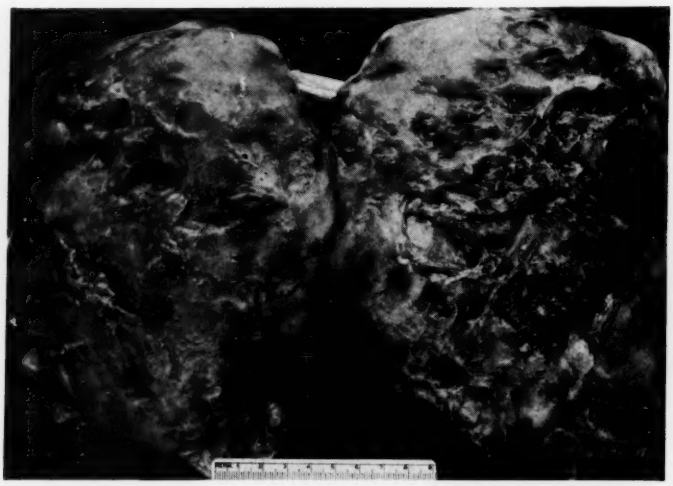

FIG. 1. SEMI-ENCAPSULATED yellowish tumor from region of right adrenal gland.

Microscopic sections made from 'living' portions of the tumor revealed a composition of polyhedral, fatty, granular cells similar in many respects to the cells of the normal adrenal cortex (fig. 2). In some regions these cells were disposed in the form of anastomosing cords and strands in an arrangement approaching that of the reticular and fascicular zones of the normal gland (fig. 3). In other regions the appearance was that of large islands of closely packed cells without special architectural design. In almost every section vascularity was a prominent feature with frequent perivascular distribution of the tumor cells. Under the high power objective the cell type was seen to be epithelial, with a central round or oval hyperchromatic nucleus and a large nucleolus. Occasionally two nuclei were observed within the same cell. One mitotic figure was found in approximately every 6 fields examined. The cytoplasm was large in amount, granular and fatty, as demonstrated by appropriate stains. Cellular outlines were sharp and the cells were for the most part polyhedral, although a few were oval. The tumor cells varied considerably in size and in lipoid content. Occasional giant cell forms were observed with nuclei almost filling the entire cell body and multiple large nucleoli (fig. 4) Departure from the appearance of normal adrenal cortical cells was such that the malignancy of the lesion was graded 2 on the basis of 1 to 4 (Broders). No trace of the normal adrenal gland of origin could be found in spite of multiple microscopic sections.

COMMENT

The evidence in this case certainly suggests that the tumor of the adrenal cortex was solely responsible for diabetes mellitus, which had been present for at least 3 years, while producing no other obvious endocrine manifestations. Glycosuria, which was not entirely controlled with large doses of insulin, and elevated values of the blood sugar constituted adequate evidence for a diagnosis of diabetes mellitus, as ordinarily defined. Removal of the tumor resulted in restoration of the patient's carbohydrate metabolism to normal, as measured by glucose tolerance tests.

It is interesting to speculate on various mechanisms by which the tumor might have produced such a profound disturbance of carbohydrate metabolism. Mechanical interfer-

ence with the normal physiologic processes of the pancreas by the large tumor mass is eliminated from consideration by the lack of evidence of deficiency of the external secretion, and the normal appearance of the pancreas when it was explored surgically. A nonspecific aggravation of latent diabetes by the tumor also seems improbable, inasmuch as latent diabetes could not be demonstrated following removal of the tumor. One is thus led to the conclusion that its mode of action was hormonal. Shepardson and Shapiro made the reasonable deduction that the presence of the 'anlage' of diabetes, or whatever it is that determines an hereditary predisposition to diabetes, is essential before the secretion of an adrenal cortical tumor could cause diabetes to become manifest. This possibility cannot be proved or disproved, although in this case there was no demonstrable underlying impairment of carbohydrate metabolism after removal of the tumor.

The absence of any of the other usual endocrine manifestations of adrenal cortical tumors leads to the supposition that the secretion of the tumor cells consisted chiefly of those adrenal cortical steroids whose effects are predominantly on carbohydrate metabolism. It may or may not have been mere coincidence that cessation of menses and the occurrence of other menopausal symptoms followed soon after removal of the growth.

Had it been possible to demonstrate a diabetogenic effect of extracts of the tumor in the patient or in experimental animals, the chain of evidence that the tumor was the diabetogenic agent would have been complete. However, previous attempts at extraction of suitable amounts of potent crude material or of steroid compounds from tumors of the adrenal cortex removed at the Mayo Clinic had been so uniformly unsuccessful that extraction of the tumor was not undertaken.

The patient's hypertension was apparently an incidental phenomenon not related to the tumor, since it persisted without change following excision of the tumor. The relationship of the patient's diarrhea to the tumor remains obscure. Studies of electrolyte metabolism and steroid excretion were not performed because the origin of the tumor from the adrenal cortex was not appreciated prior to operation.

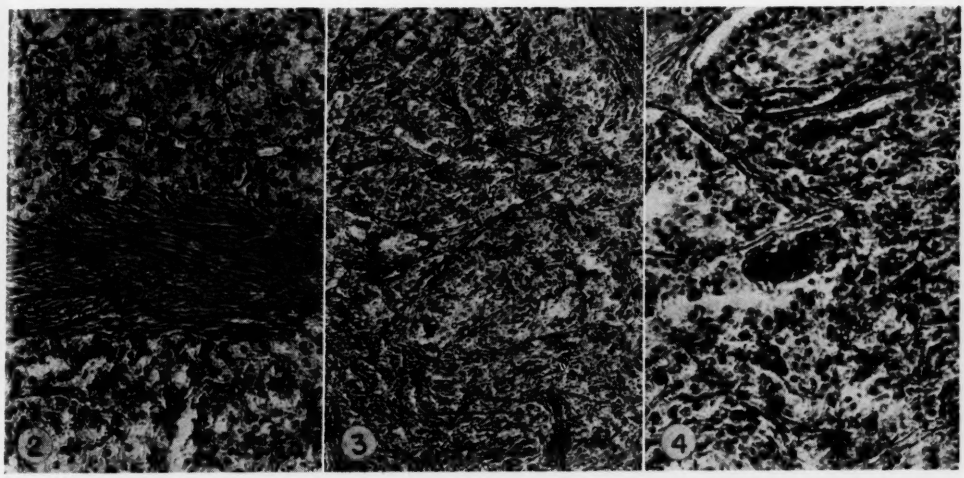

FIG. 2. GRADE 2 ADENOCARCINOMA. Note the strong resemblance of these fatty, granular tumor cells to the polyhedral cells of the normal adrenal cortex. Hematoxylin and eosin; ×200.

FIG. 3. GRADE 2 ADENOCARCINOMA. The arrangement of the tumor cells in strands, cords and columns recalls the disposition of normal adrenal cortical elements. Hematoxylin and eosin; ×90.

FIG. 4. GRADE 2 ADENOCARCINOMA. Note the large multinucleated cell in center of the field. These malignant giant cells are fairly characteristic of adrenal cortical carcinomas. Hematoxylin and eosin; ×200.

SUMMARY

A case is presented of a woman in whom a severe disturbance of carbohydrate metabolism having the characteristics of diabetes mellitus, unaccompanied by other obvious endocrine abnormality, disappeared completely following the removal of a large tumor arising from the cortex of the right adrenal gland.

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Control of Diabetes Mellitus

HENRY J. JOHN, LT. COL., M.C.

From the Lawson General Hospital, Atlanta, Georgia

THE EFFORT to treat diabetes alone without taking into consideration the individual harboring the disease will fail. The disease and its possessor are closely allied and must be considered together in the planning and execution of the diabetic routine.

The restoration of normal body functions is the goal of sound therapeutic procedure. In the treatment of diabetes the attempt is made to restore the waning insulogenic function. Diabetes means but one thing: insufficient insulin production. When infection occurs there is an added factor, namely the blocking of insulin action so that a unit of insulin does not exert the same effect as it does when infection is not present. This may not always happen, for patients may undergo serious infections without the necessity of increasing the dosage of insulin. A case in point is that of a diabetic who developed a severe lobar pneumonia; empyema followed and had to be drained. Not only was it unnecessary to increase the insulin, but it actually had to be reduced and finally stopped. Two years later it was necessary to resume the insulin therapy. Such cases, however, are exceptions and not the rule.

When confronted with a new case of diabetes we know that there is insufficiency of endogenous insulin which is manifested through hyperglycemia and glycosuria. Enough exogenous insulin will have to be supplied each day to compensate for this deficiency. This may be as little as 10 or as much as 80 units. Since it is not known at the start just how much insulin a particular individual will require the medical problem is to determine the amount necessary to control the hyperglycemia and to eliminate the glycosuria.

Submitted by request, Oct. 30, 1942.

If the patient's hyperglycemia is controlled throughout the day, the glycosuria, ketosis and polyuria are automatically controlled.

In the treatment of diabetes the pathologic changes which the pancreas is undergoing must be borne in mind: *a*) the early changes in the beta cells of the islands of Langerhans, the loss of granulation, the swelling and vacuolation; *b*) some 30 to 90 days later (barring infection which speeds up the process) the stage of cell degeneration with its hyaline degeneration and beginning fibrosis. The first stage is reversible, the second stage is irreversible. When these pathologic processes are kept in mind, the therapeutic procedure becomes obvious, i.e. the quick control of hyperglycemia. Hyperglycemia aggravates the diabetic condition in that it favors the progressive degeneration of the beta cells which, if continued, results in irreparable damage. Experimental work has shown such transitions brought about by hyperglycemia. The important point is not how the patient feels but what is happening to the pancreas. The routine instituted should restore physiology to normal or near-normal and if it does, the patient will feel well and the progression of the pathologic process in the pancreas will stop.

The time to use insulin, and in ample dosage, is at the time of discovery of the diabetes, realizing that hyperglycemia, if allowed to continue will destroy the beta cells which secrete insulin. Changes are already present in many of these beta cells, but at this time, these changes are in the first stage, the reversible stage. By proper treatment most of these islands can be restored to normal function. The proper secretory function of the beta cells which have reached the second or irreversible

stage is lost. Since every day counts, control of the hyperglycemia must be accomplished quickly. The rapid control results in the early discharge of the patient from the hospital.

Diet. An adequate diet from the start is important so that the patient feels satisfied. At Lawson General Hospital, a diet consisting of

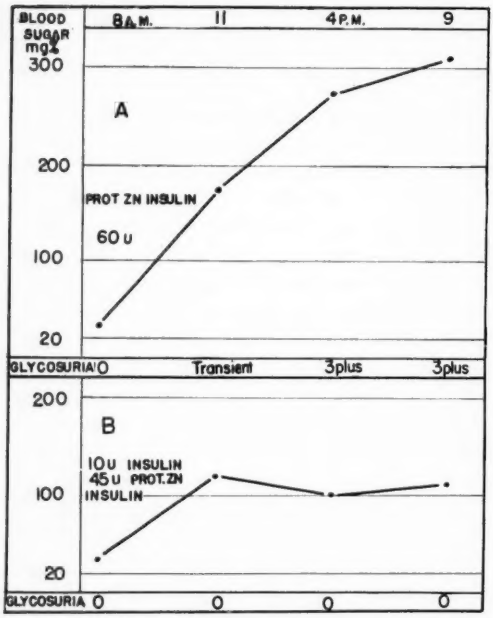

FIG. 1. *A*. Blood-sugar rise and glycosuria following 60 U of protamine zinc insulin and the 3 meals. The blood-sugar figures taken from the data of Tolstoi et al. Note the continued hyperglycemia throughout the day. *B*. The same with redistribution of insulin: 45 U of protamine zinc insulin and 10 U of insulin, both given before breakfast. It is the quick-acting insulin which prevents the post-breakfast hyperglycemia, and as its action diminishes protamine zinc insulin maintains the lowered blood-sugar level.

200 gm. of carbohydrate, 100 gm. of protein, 100 gm. of fat, a total of 2100 calories is used. This is adequate and easy to follow since a patient on such a diet will soon be able to select meals, provided he is taught to measure the portions of his food by the ordinary measures of spoon and cup.

Insulin. How much? How to divide it? Since we do not know at the start how much insulin a patient will require it is largely a guess at the beginning of treatment. If the original blood sugar value is high, 20-10-20 units per day may be given. If the blood sugar is not high, 15-5-15 U may be adequate. A daily 24-hour quantitative urine sugar determination is essential throughout hospitalization and the estimation of blood sugar 3 times a day before eating is no less important. With this information we can proceed rapidly and with precision. If the rationale for this procedure is explained to the patient he will coöperate as it means the saving of time and expense for him.

Protamine zinc insulin. Because about 85 per cent of the cases of diabetics can be controlled by one daily injection of protamine zinc insulin it is naturally the insulin of choice. When a change is made from insulin to protamine zinc insulin, the slow action of protamine zinc insulin must be taken into account. For instance, a patient in whom hyperglycemia has been well controlled on 20-10-20 U of insulin may have a hyperglycemia persisting more or less all day after receiving 50 U of protamine

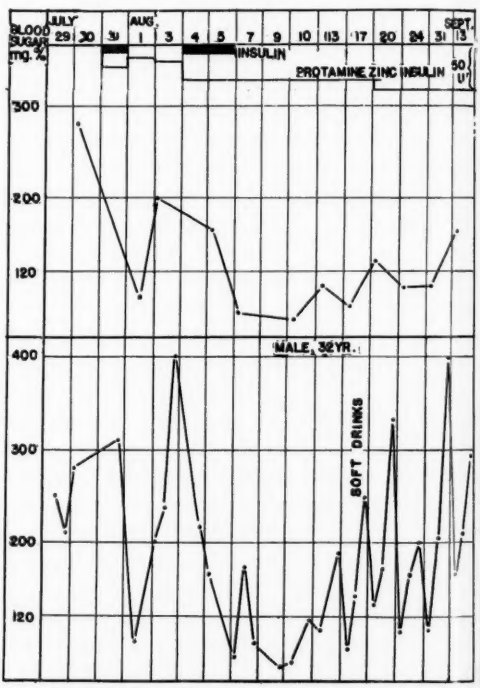

FIG. 2. Progress of a diabetic on a fixed diet, the insulin alone being varied according to indications. The upper half of the chart represents only the fasting blood sugars; the lower half the morning, noon and evening blood sugars. From this chart it is clear that if one has only the fasting blood-sugar data, the curve not only does not tell the whole story but may be actually misleading.

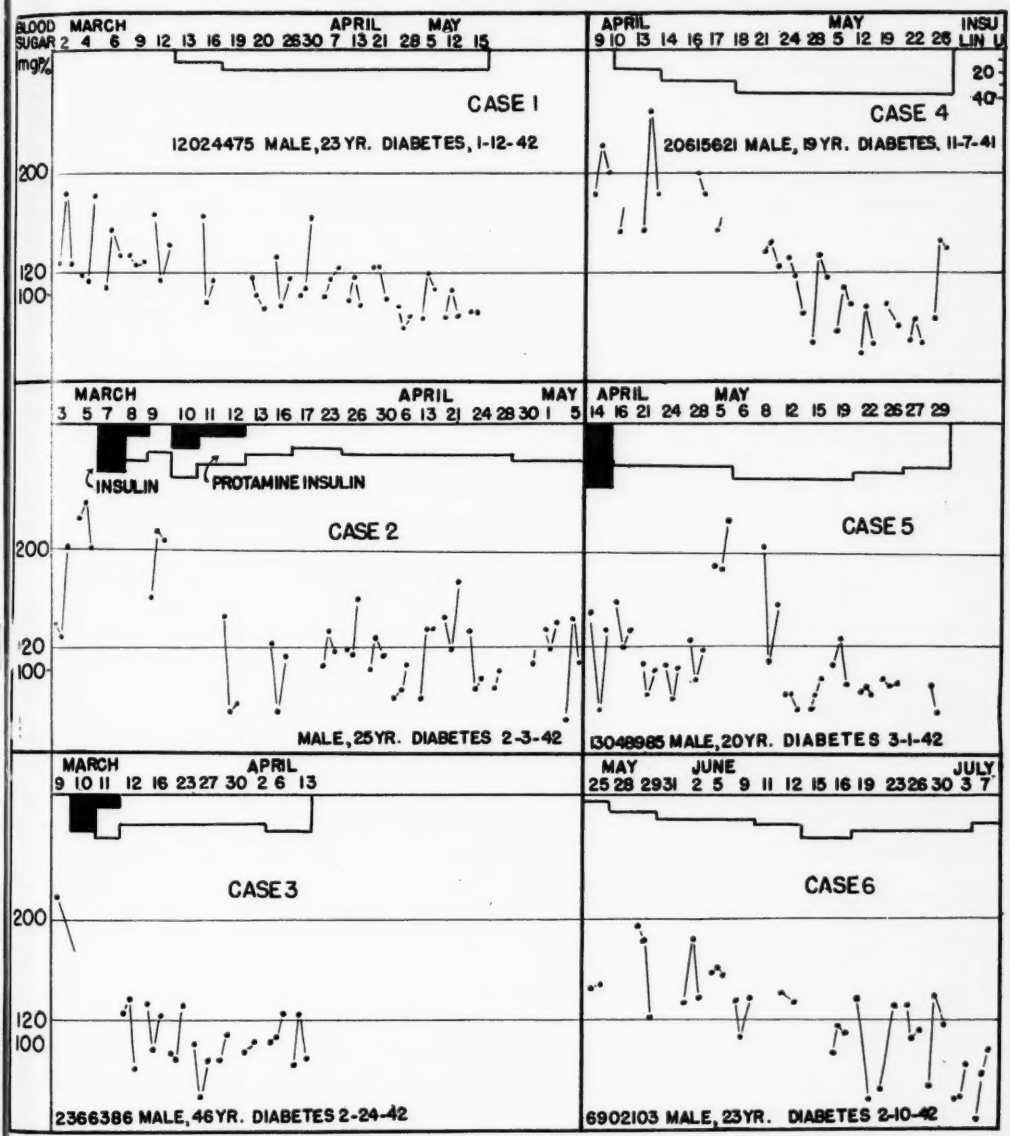

FIG. 3. Progress of 6 soldiers with diabetes for whom the 3 blood-sugar determinations per day serve as the guide to insulin therapy. In this manner one knows at all times how a routine is working. Also note the effect of infection on the blood-sugar level in *case 5*, May 5th.

zinc insulin and ingestion of the heavy breakfast (fig. 1A). This rise can be anticipated and 10 U of insulin can be given in addition, either immediately before or after breakfast, in order to prevent the hyperglycemia (fig. 1 B). This addition of insulin may be necessary only on the first day. After that the 50 U of protamine zinc insulin in the morning is adequate.

Supposing, however, the patient receiving the 50 U of protamine zinc insulin and 10 U of insulin has a reaction the next morning. It will then be necessary to reduce the protamine zinc

insulin dosage to 45 or 40 U which will correct the morning hypoglycemia. Again, this reaction may not occur the first day, but 3 to 5 days later. The same principle applies. If, on 40 U of protamine zinc insulin the morning blood sugar is 60 or 70 mg. per cent and the 24-hour-urine sugar is heavy (fig. 1A), the diabetes is not controlled. If the blood sugar is determined morning, noon and night the figures will be such as these: 60-394-300 mg. per cent. With this type of blood-sugar level it is clear that the patient is hyperglycemic some 18 of the 24 hours. Only the morning blood sugar is low and the persistent hyperglycemia during the rest of the day is both abnormal and damaging. If the normal period of postprandial hyperglycemia is 6 of the 24 hours (2 hours after each meal) then the treatment accorded the patient is not only inadequate but harmful. The proper way in which to gauge insulin dosage is to make blood-sugar determinations 3 times a day, before meals. By so doing the addition or subtraction of insulin may be made. Fasting blood-sugar determination may tell but a small part of the story, and, in fact, may be misleading (fig. 2).

Suppose that with 40 U of protamine zinc insulin the blood sugars are 60-394-300 mg. per cent throughout the day. How can the hyperglycemia be changed to approximately normal blood-sugar values throughout the day? It is obvious that the dosage should not be increased, for this would undoubtedly produce a hypoglycemia with a severe reaction the following morning. Since the blood sugar is normal or low each morning, the total dosage should not be increased above 40 U. In this situation 30 U of protamine zinc insulin and 10 U of insulin, both given before breakfast would probably give the desired result. This method of administration will lower the hyperglycemia throughout the day; 25 U of protamine zinc insulin and 15 U of insulin or other adjustment of dosage may be necessary. In this manner, therefore, not only the hyperglycemia, which is harmful, is eliminated but also, automatically, the glycosuria is either entirely abolished or reduced to a few grams per day. Thus a normal or near-normal glycemia throughout the 24 hours and sugar-free urine (or less than 10 gm. in 24 hr.) is considered the ideal and ultimate goal to strive for in the control of diabetes.

In some cases the protamine zinc insulin and the insulin can be given in one syringe. This has worked well at times; however, one must find out if it actually does work and only then adopt this method. Another point of importance in patients receiving only one injection of protamine zinc insulin per day is that the breakfast should be a small meal in order to prevent the marked rise of blood sugar following breakfast.

Mental reactions of the patient. It is a blow to a layman or a physician to be told that he has diabetes. He either knows nothing about diabetes, or there may be a distressing familial history of the disease. These are disturbing thoughts for anyone. The best thing for the mental outlook of the patient is to give him a manual on diabetes written in the language of a layman. He will probably become intensely interested, for he will be finding out something about the disease written authoritatively for him. No longer has he the horror of his condition but begins to see the rationale of the treatment prescribed. The dietitian supplies further instruction about diet, the nurse instructs him in the technic of insulin injections, not with a hospital syringe, but with one of his own (the B. & D. outfit in which the syringe, after preliminary boiling, is kept in a tube of alcohol and has to be sterilized only about once a month is very practical).

The patient should not be kept in bed but should be up and about, active, taking normal exercise or going to the theater; there is no danger of a reaction when he is taking protamine zinc insulin for, if a reaction occurs, it will probably be between 4 and 7 A.M. The muscles as well as the mind should be occupied. This exercise is essential, for, if a patient is kept in bed, the routine and insulin dosage will be calculated only for the inactive stage and thus will be incorrect. A diabetic patient should be up and about, simulating the activity of his normal life so that the diet and insulin dosage may be adequately determined for him as he goes about his usual duties.

Endocrine Aspects of Hypertension

MAX A. GOLDZIEHER, M.D. AND
S. SALMOVITZ, M.D.

From the Endocrine Clinics of the Brooklyn Women's Hospital and the Stuyvesant Polyclinic, New York City

CURRENT emphasis upon renal and nervous factors in the genesis of hypertension tends to distract attention from the fact that high blood pressure is also a concomitant of various endocrine disorders.

Myxedema frequently gives rise to hypertension (unless prevented by cardiac dilatation) and this is promptly relieved by thyroid medication (1). The early stages of clinical hyperthyroidism are also frequently marked by increase of the systolic pressure and of pulse pressure which are commonly normalized by appropriate treatment of the thyroid disorder.

In diabetes mellitus the incidence of hypertension from the 35th year on is high and increases with age (2).

High blood pressure is common in both men and women at the stage of life when the sex hormones are on the wane.

The relationship of pituitary disease to hypertension is less well defined although neoplasms of this gland are often associated with elevated pressure irrespective of whether acromegaly occurs or not. Claims are not lacking that the hypertension of the toxemia of pregnancy is linked with abnormal functioning of the posterior lobe of the pituitary although the evidence is not conclusive.

That the adrenal glands play a part in clinical hypertension is unquestioned. The occurrence of paroxysmal hypertension with pheochrome tumors, and its subsidence with excision of the neoplasms affords definite proof of the relationship to adrenalin production. Although questioned by some, it is our belief that nodular or diffuse hyperplasia of the adrenal medulla is also often causally associated with non-paroxysmal hypertension (3). Direct evidence of the relationship is seen in the hypertrophy of the musculature of the adrenal veins (4, 5, 6).

Of recent years the association of adrenal cortical tumors or hyperplasia with hypertension has aroused increasing interest. High blood pressure is an outstanding symptom of Cushing's syndrome, originally described as pituitary basophilism, although this disease is more consistently associated with hyperplasia or tumors of the adrenal cortex than with a basophile adenoma of the pituitary.

Conversely, destruction or removal of the cortex causes hypotension. This is one of the most consistent symptoms of Addison's disease and readily yields to the administration of potent cortical extracts. Such extracts, in our experience, are also effective in normalizing the blood pressure in cases of peripheral circulatory collapse occasioned by shock, trauma, burns or acute infections in which impairment of the adrenal cortex is practically always demonstrable.

The association of such diverse endocrine conditions with disturbance of blood pressure can hardly be ascribed to any single substance. It might, however, be possible to find in metabolic concomitants some common denominator. This we have sought.

The adrenal cortex plays an important rôle in regulating salt and water metabolism. Adrenalectomy and Addison's disease are accompanied by loss of sodium chloride and water, which inevitably leads to death unless corrected either by supplying sodium salts and

Received for publication September 18, 1942.

water, or by the administration of potent cortical extracts. Excessive dosage of such extracts —and particularly of desoxycorticosterone acetate—produces salt and water retention which may be followed by edema, hypertension and cardiac failure. The typical changes of the blood electrolytes in Addison's disease (low sodium, high potassium) are accompanied by hemoconcentration, low blood volume and low blood pressure, in striking contrast to the findings in hypersecretory cortical tumors. In Cushing's syndrome or in other types of adreno-genital disease the opposite relationship of blood electrolytes obtains: high sodium and decreased potassium, accompanied by plethora and hypertension. The correlation between salt and water retention, on the one hand and hypertension on the other, suggests the possibility that a similar mechanism might be at work, not only in cortical hyperactivity but also in other hypertensive states in which adrenal function is apparently normal but in which other endocrine disorders are prominent.

Retention of sodium, chloride and water is a characteristic feature of hypothyroidism. The urinary output is reduced without evidence of renal insufficiency (8), while the almost constant achlorhydria further decreases the elimination of chlorides. 'Administration of thyroid produces a diuresis of impressive proportions; water and salts move from intracellular spaces into the blood stream and out through the kidneys' (1).

The situation is more complex in hyperthyroidism: the loss of sodium, chloride and water in the course of increased perspiration and frequent diarrhea leads to a decreased blood volume which might well account for the low diastolic pressure. The increase in systolic pressure seems to be based on a different mechanism perhaps abnormal irritability of the sympathetic nervous system.

A common feature links hypertensive cases of diabetes, climacteric and various types of pituitary disease into one group: the increase in blood pressure is usually accompanied by obesity. Much of this extra weight is furnished by an increased water content of the body, hence administration of diuretics as well as restriction of salt and water intake are well recognized means of weight reduction. The customary weight-reducing diets, moreover, are rich in protein and poor in carbohydrate, therefore improving diuresis, in contrast to the oliguria noted on unrestricted food intake. Episodes of water retention occur in women prior to, or during menstrual periods, which accounts for sudden, often startling, though ephemeral, gain in weight. Loss of water from the tissues and decrease of the body fluids immediately available for circulation is accompanied by a drop of the systolic and especially the diastolic blood pressure.

Impressed by the prevalence of salt and water retention in various endocrinopathies and by the well-known rôle of retention in high blood pressure, we have investigated, systematically, for the past 8 years, all patients afflicted with hypertension, irrespective of its association with any particular endocrinopathy. Our aim was to devise simple methods for the recognition of salt and water retention, as well as to determine if procedures instituted to adjust the metabolic disorder would prove beneficial in the treatment of hypertension. We have tabulated a series of 100 unselected cases which came under our observation with various complaints including menstrual disorders, menopause, obesity, hirsutism, diabetes and thyroid disease. The group comprised patients of all ages from 15 to 69 years. Eighty-four were females.

Retention of salt and water was gauged by the salt-tolerance test. Twenty-four-hour urine specimens were collected on 2 consecutive days during which patients were kept on identical food and liquid intake. On the second day, after breakfast, 10 grams of sodium chloride and 250 cc. of water were administered. The urine and sodium chloride output on these two days was compared. Additional information was obtained by determination of blood chlorides, separately estimated on the whole blood, plasma and red cells.

It was found that the majority of the patients (71%) retained water; the water retention exceeded the extra amount administered (250 cc.) in 48 per cent of the cases while the amount retained for the entire group of 100 patients averaged 167 cc. Salt retention was demonstrable in 83 per cent; the amount retained exceeded the amount administered in 14

per cent and for the 100 patients averaged 6.3 grams of salt.

The blood-chloride values for whole blood, and plasma, while occasionally increased, averaged 495 and 587 mg. per cent, respectively, and are well within the normal range. The average value for chlorides in the red blood cells (390 mg. %), however, is definitely high. As a rule, the degree of urinary salt retention and the level of the red blood-cell chlorides were parallel, although absolute uniformity did not obtain.

The conclusion to be drawn from this analysis of cases of hypertension was that salt and water retention must be corrected. The management of our patients who were all ambulatory, included diet, medication and endocrine therapy. The dietary management was based on the observation that the blood pressure of hypertensive, obese patients often decreases during weight reduction without other treatment. All hypertensive patients retaining salt and water were given the high protein, low carbohydrate diet, restricted in salt and liquid intake which is used for weight reduction. Underweight patients received adequate supplements of fat to prevent weight loss.

Medication consisted, primarily, of ammonium chloride (7.5 grain, in enteric coated tablets, *t. i. d.*), for the purpose of increasing urinary excretion of sodium chloride. The medication was changed after 5 days to potassium acetate or some other organic potassium salt in order to increase elimination of chlorides in the form of both sodium and potassium salts. Considerable quantities of salt are removed by this alternating medication, which is accompanied by a significant reduction in the level of both chloride and sodium values of the blood.

Correction of water and salt retention without other treatment is often successful in reducing the elevated blood pressure. Favorable response in a greater percentage of cases and to a larger degree is obtained with the addition of sedation. For this purpose we used the combination of atropine sulphate, (1/300th to 1/150th) and phenobarbital (0.25 to 0.5 grain) *b. i. d.* The use of sedatives was limited to the initial period of the treatment. Endocrine therapy, according to individual needs, further improves the results. Thyroid medication in cases of hypothyroidism, and sex hormones in the climacteric are adjuvants of obvious value. Unfractionated pituitary extracts parenterally were used for the treatment of menstrual disorders. Of particular value, however, was the posterior pituitary extract. Notwithstanding the temporary period of antidiuresis following injection of these extracts, this initial phase was soon superseded by increased diuresis accompanied by greater elimination of chlorides.

TABLE 1. SALT TOLERANCE TEST IN SERIES OF 100 PATIENTS WITH HYPERTENSION

Test Dose, 10 gm. NaCl; 250 cc. H_2O	First Day	Second Day	Retention
24-Hour-Urine, Av. cc.	1253	1356	167 (250–83)
Average NaCl, gm.	8.7	12.8	6.3 (10.0–3.7)

TABLE 2. FREQUENCY OF WATER AND SALT RETENTION IN SERIES OF PATIENTS WITH HYPERTENSION

	Water	Sodium Chloride
Retention, Occurred in	71%	83%
No retention	29%	17%
Retention in excess of test dose	48%	14%

TABLE 3. CHANGES OF WEIGHT AND BLOOD PRESSURE IN 100 CASES OF HYPERTENSION

	Average Weight, lb.	Average Blood Pressure, mm. Hg	
		Systol.	Diastol.
Before treatment	193	179 (132–245)	103 (100–140)
After treatment	168	142 (110–210)	84 (62–130)

The results of these therapeutic efforts were striking. The 100 patients lost an average of 25 pounds with a maximum of 73 pounds in one case. The 6 underweight patients, included in the series, gained a total of 34 pounds, an average of 5.5 pounds. The mean blood pressure of the whole group after treatment was calculated at 142/85 mm. Hg, as compared with 179/103 before the treatment. Therapy failed in 3 cases, including one patient observed for 8 years, who had not heeded earlier advice to seek surgical relief. The two other cases were treated for only 2 and 4 months, respectively, and their coöperation was questionable. The time of treatment and observation for the whole group averaged 13 months.

SUMMARY

The relationship between abnormal blood pressure and varied endocrinopathies is reviewed. Disturbances of salt and water metabolism are demonstrable in the diseases reviewed and show a coincidence of hypotension and a loss of salt and water on the one hand and of hypertension and retention of salt and water on the other.

The results of study of a series of 100 hypertensive patients are presented. The data demonstrate the association of salt and water retention and hypertension in the endocrine patients. Increased values for red-blood-cell chlorides were also obtained.

Treatment of these patients with dietary and medicinal methods aimed at relief of the retention phenomena, produced a considerable drop of blood pressure which was maintained during a prolonged period of observation. The clinical results were improved by the addition of sedation in the ambulatory patient and by appropriate endocrine therapy.

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A Comparison of Methods Used in Determining the Time of Ovulation[1]

FRED E. D'AMOUR, Ph.D.

From the Biologic Research Laboratories, University of Denver, Denver, Colorado

ALL INDIRECT METHODS used in attempting to determine the time of ovulation in women are open to the criticism that it is not ovulation, but something else, which is being studied. On the other hand, such direct methods as the inspection of ovaries at laparotomy, and the recovery of eggs from the tubes, also have their shortcomings. In addition to the limitations imposed by the necessary surgical procedures, the direct methods usually permit only one observation on a given subject, they give little information of underlying physiologic mechanisms and they are not entirely objective, as the interpretation of the stage of development observed rests on the judgment of the investigator. Indirect methods, therefore, have their place, in spite of fundamental weaknesses and what is required is the establishment of their validity as tests for ovulation.

It is now generally accepted that ovulation usually occurs during the mid-interval of the menstrual cycle, and that it is under hormonal control. The length of the mid-interval, the frequency of non-ovulatory cycles, and whether ovulation may occur more than once in the interval between menstrual cycles is not known. Further knowledge concerning the details of physiologic control is also highly desirable. It is to such problems as these that many studies, by indirect methods, are being turned.

Received for publication September 30, 1942.

[1] This study was supported in part, by a grant from the Committee on Research in Endocrinology, National Research Council.

The degree of validity of any result obtained by indirect methods in the study of ovulation depends upon the degree of truth of the assumption that the observed phenomenon is an index to the activity in an unobserved structure, namely the ovary. The better established this relation, the stronger is the evidence. This relationship may, on the basis of present physiologic knowledge, be considered well established for 4 methods. These are *a*) gonadotropin assays, because hypophyseal activity governs ovarian function; (*b*) estrogen assays, because the ripening follicle produces estrogen; *c*) pregnanediol determinations, because its precursor, progestin, is formed by the corpus luteum after ovulation; *d*) vaginal smears, because the vaginal epithelium is altered in response to ovarian hormones. Further, if the results of several indirect methods, related to each other in terms of known physiology, all show some pronounced deviation from the norm during the mid-interval it strengthens, mathematically, the chance that each is, in fact, related to ovulation itself.

Not as strong a case can be made for methods in which the relationship to ovarian function is less clear. Cyclic changes in body temperature, for instance, are more difficult to evaluate, and the same is true of alterations in electric potential and hemoglobin reduction. Subjective experiences are most unreliable of all, because of their vagueness and variety. However, if by one of these latter methods a definite change were recorded at a time when

ovulation was indicated by one of the 4 more specific indirect methods, the results might be acceptable, and the nature of the relationship could be left for later elucidation.

The purpose of this study was to compare, on the same 20 cycles, results obtained by 6 indirect methods for the study of the time of ovulation, namely, gonadotropin assays, estrogen assays, pregnanediol assays, vaginal smears, body temperatures and subjective experiences. For technical reasons not all methods could always be used during the same cycle, but at least 4 were employed for each cycle studied. The basic assumption that ovulation usually occurred during the mid-interval and was under hormonal control was accepted as a starting point; it was thought that comparison of the results obtained from studies made at this time would either strengthen or weaken the validity of each method as a suitable test for ovulation. It was also hoped that determination of the time-sequence of different happenings, in relation to each other, might furnish information as to the mechanisms underlying them.

More than mere formal acknowledgment of indebtedness is due the five subjects whose cooperation made this study possible. The daily task of collecting complete 24-hour urine specimens, making vaginal smears and recording body temperatures, over periods of 3 to 5 months, is not pleasant.

EXPERIMENTAL METHODS

The assay methods used in this study are more or less standard and need not be described in detail. Complete 24-hour specimens of urine were collected, chloroform added as preservative and kept in the refrigerator. No sample stood more than 48 hours before being used.

Gonadotropin. Determination of gonadotropin, which does not interfere with the estrogen or pregnanediol determination, was made in all cycles. Levin and Tyndall's method (1) was employed, using 26-day-old rats as test animals. Details of the method, as used by us, have been published previously (2). A dose of precipitate, representing 3 hours excretion of urine, was given to each of 4 rats, this dose having been found in previous studies to be best suited to show peaks in excretion. When the response was positive, the dose was reduced one-half. In some cycles the study was more thorough, the assay for the entire cycle being repeated, using a double dose of the precipitate.

Estrogens. We were unable to develop a satisfactory method for the determination of both estrogen and pregnanediol from the same urine. In order to determine both for the same cycle it was, therefore, necessary to pool the urine. Following precipitation of gonadotropin, one-half the sample was assayed for estrogen, the other half, plus one-half of the next day's urine, being used for pregnanediol determination. This weakens the assay for estrogen, only half of the sample being available. For some cycles, therefore, estrogen alone was determined. The method included acid hydrolysis, extraction with chloroform, transfer to olive oil and injection into castrated female rats. The urines for one cycle of each subject were assayed for both estrone and estriol, using the method of Cohen and Marrian (3). For another cycle of each subject no estrogen determination was made, all urine being used for pregnanediol.

Pregnanediol. When both estrogen and pregnanediol were determined for the same cycle, the method of Venning (4) was usually employed for the latter; if pregnanediol alone was determined, both Venning's and Astwood's (5) methods were used. The latter method is somewhat less tedious but both are time-consuming and neither yields a product which is entirely pure. A titrimetric method has recently been reported by Allen and Viergiver (6). It has not been used in this study, however. Some workers allow for impurities on the basis of reduction in melting point. It seemed somewhat more accurate to determine the average weight of impurities (usually between 1 and 2 mg.) on samples run during the first half of the cycle and subtract this weight from those containing pregnanediol. Obviously this introduces an error and the figures are not accurate. However, the amount of crystals which are visible permits a fairly good qualitative check.

Vaginal smears. The details of the method used are described by Rubenstein (7). Smears were made in duplicate. The staining technic of Shorr (8) provided uniformly good material.

Body temperature. Vaginal temperatures were taken daily before arising.

Personal observation. Each subject kept a note book for recording phenomena. As a guide for observation, the headings used in chapter

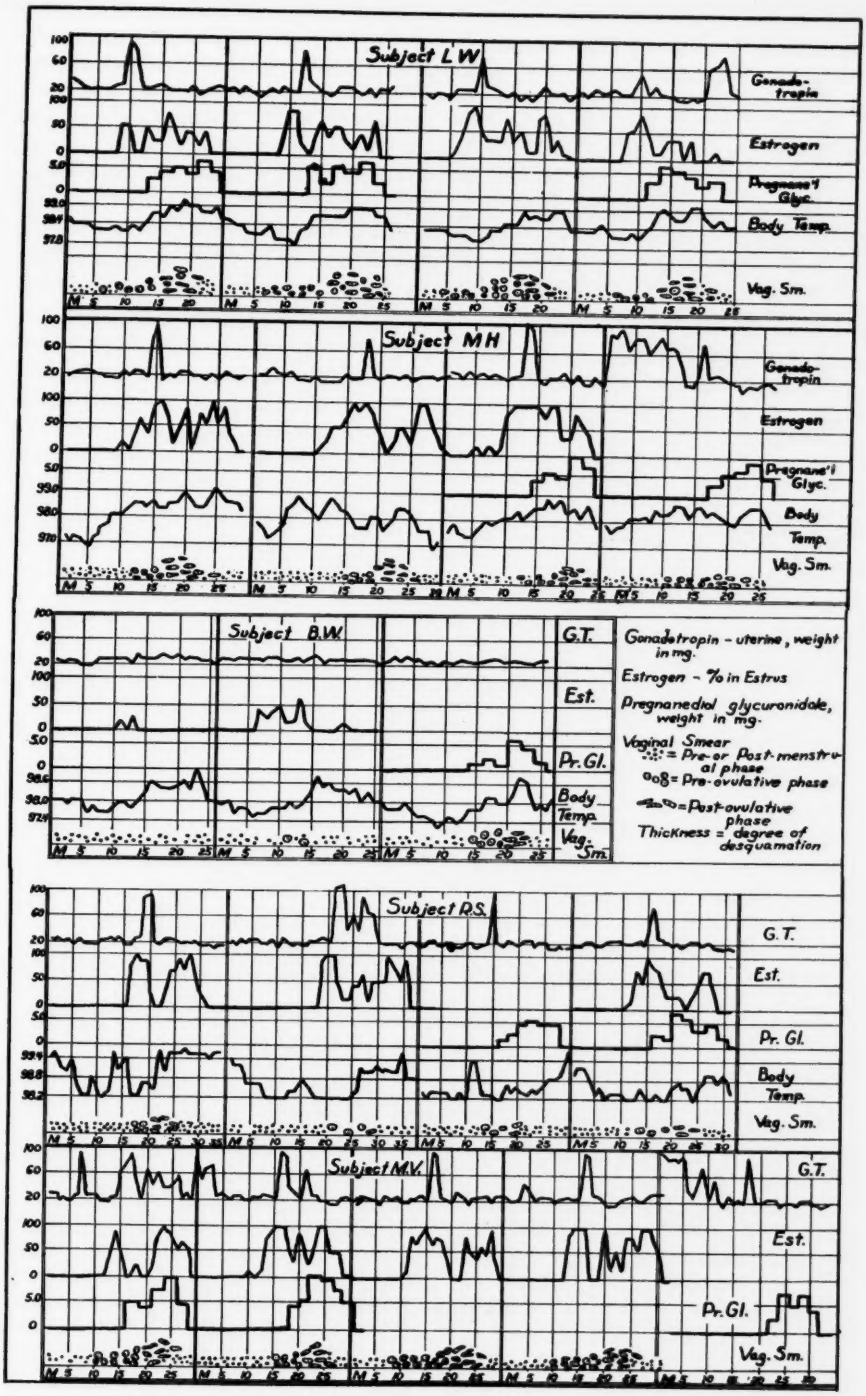
Subject L W
Gonado-tropin
Estrogen
Pregnane'l Glyc.
Body Temp.
Vag. Sm.
Subject M H
Gonado-tropin
Estrogen
Pregnane'l Glyc.
Body Temp.
Vag. Sm.
Subject B.W.
G.T.
Est.
Pr. Gl.
Body Temp.
Vag. Sm.
Gonadotropin - uterine, weight in mg.
Estrogen - % in Estrus
Pregnanediol glycuronidate, weight in mg.
Vaginal Smear
= Pre-or Post-menstrual phase
= Pre-ovulative phase
= Post-ovulative phase
Thickness = degree of desquamation
Subject R.S.
G.T.
Est.
Pr. Gl.
Body Temp.
Vag. Sm.
Subject M.V.
G.T.
Est.
Pr. Gl.
Vag. Sm.

FIG. 1

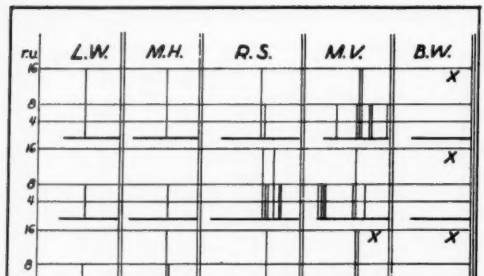

FIG. 2

10 of 'Time of Ovulation in Women' (9) were followed.

RESULTS

Since it was not possible to obtain data for all cycles with the same degree of completeness, the data are arranged in two groups of graphs. Figure 1 provides a comparison primarily of subjects, on the basis of data of equal strength. The remaining graphs include the data for the more thorough assays and, therefore, give information of greater quantitative reliability on the actual amounts of hormone excretion. For instance, all gonadotropin data shown in figure 1 are based on the same type of assay, namely a dosage of precipitate equivalent to a 3-hour-urine excretion administered to each of 4 rats, thus making possible a comparison of all cycles on data of equal adequacy. Figure 2, however, provides more complete data on gonadotropin excretion for some cycles, since it includes those in which the assay was more extensive. In the same way, since it was not possible to assay the urine in each cycle for estrogen at two dosage levels, figure 1 gives the result for each cycle at the same assay level, namely a dosage equivalent to a 1-hour-urine excretion. Figure 3 presents the results of the more extensive assay and also of assays for both estrone and estriol. Figure 1 shows the results for pregnanediol in comparable terms, that determined by the Astwood method having been calculated as pregnanediol glycuronidate. Figure 4 provides more complete data on this subject, giving results obtained by both the Venning and Astwood methods.

In figure 1 the data on body temperature and vaginal smear changes are recorded. The ap-

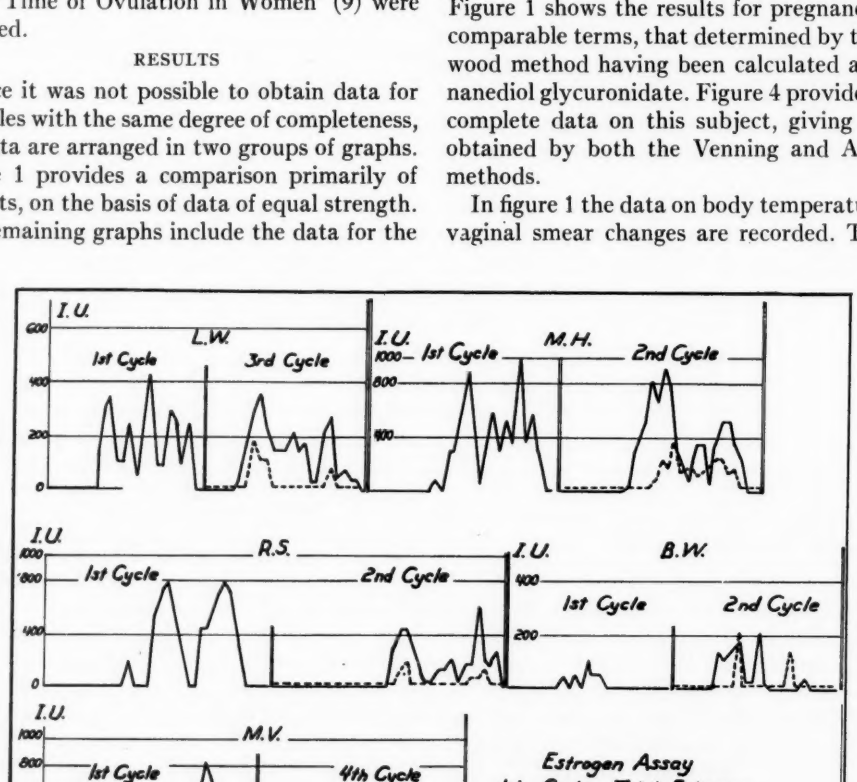

FIG. 3

pearance of those cell types reflecting estrogenic activity (pre-ovulatory phase, according to Rubenstein) is indicated by circular, nucleated cells; that of cells produced by action of the luteal hormone (post-ovulatory phase) by flattened cells. The relative intensity of the response to hormonal stimulation is indicated by the number of cells drawn. Dots represent both pre-menstrual and post-menstrual smears. The degree of desquamation is indicated by the thickness of the graph.

No attempt was made to include information concerning subjective experiences in the graph; these are described later.

DISCUSSION

Inspection of figure 1 gives a distinct impression of rhythmicity in the recurrence of phenomena, but a more careful examination shows many exceptions. However, because of the general uniformity of the curves there appears to be a 'normal' pattern. This normal pattern for gonadotropin excretion is a peak in the mid-interval of the cycle; for estrogen excretion, a double wave; for pregnanediol, a continued excretion during the luteal phase; for body temperature, a rise from a low to a high level somewhere during the mid-interval, and for vaginal smears, phasic changes in cell type reflecting estrogen and progestin stimulation.

Description of Subjects and Comparison of Cycles

Subject L. W. is 43 years old, married and the mother of 3 children. She has been the subject of previous studies (10). Three of the 4 gonadotropin curves are normal, the fourth showing a second, late peak. Estrogen and pregnanediol excretion, body temperature and vaginal smears are normal. Indications of the pre-ovulatory phase precede by a few days the assayed appearance of estrogen in the urine; this may be due to a time-lag in excretion or to the fact that the amount was too small to be demonstrated earlier. The rise in body temperature appears to be correlated with pregnanediol excretion and occurs somewhat later in the cycle than usually reported.

Subject M. H., 39 years old, married, but childless. She expressed doubt of her fertility since pregnancy has not occurred. With a few exceptions, however, the data from her cycles appear to be normal. Gonadotropin peaks appeared at the regular time, but there was an almost continuous excretion of gonadotropin during the first half of the fourth cycle, preceding the mid-interval peak. Only one of the body temperature curves shows the mid-interval rise, considered to be characteristic. The last vaginal smear showed very little desquamation as compared with the previous ones, although the pregnanediol output was normal. Except for the body temperature, the remaining data for 3 of the 4 cycles are certainly normal and insofar as they represent indices of ovulation, the sterility cannot be ascribed to failure of that function. Since there was no particular desire for children no studies were made of the husband.

Subject R. S., 25 years old, married but childless. Pregnancy has been avoided because of economic circumstances. Examination of the graph shows several departures from the assumed standard patterns. There was a double peak in gonadotropin output during the second cycle, the body temperature curve was inconsistent and the vaginal smear reaction for the last three cycles was extremely weak. There were very few of the cell types indicative of either estrogenic or luteal

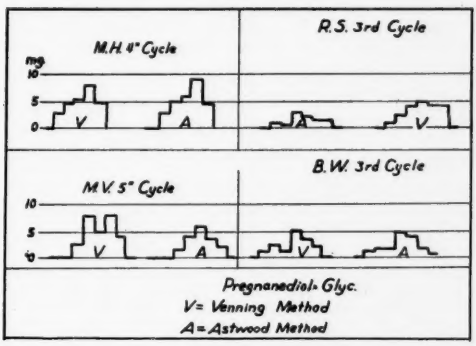

FIG. 4

stimulation and there was almost no desquamation; the pregnanediol output was somewhat less than in other subjects.

Subject M. V. is 33 years old, married but childless. The gonadotropin curve appears to be irregular, but assay at lower doses (fig. 2) shows the presence of peaks at the expected times. The results in the last cycle, however, are irregular in that there is a definitely high plateau of gonadotropin excretion during the early part of the cycle, comparable to the fourth cycle of *M. H.* The values for estrogen and pregnanediol are high and are reflected in the profuse vaginal proliferation and desquamation. Unfortunately body temperature data were not obtained for this subject. With the exception of gonadotropin in the fifth cycle, these determinations indicate normal hormonal excretion, but at a level somewhat higher than average. The fifth cycle is not consecutive with the previous 4; in all other cases, for all subjects, the cycles are consecutive.

Subject B. W. is the daughter of *L. W.* She is 22 years old, had one child, born 9 months before this study began. This study occupied the period from May to August, 1941. No gonadotropin could be demonstrated in the first two cycles, but assay at higher dosage (fig. 2) showed a small peak in the third. Estrogen excretion was very low during the first two cycles and the vaginal smear throughout remained characteristic

of the post-menstrual phase. The body temperature curve shows most typically the accepted form for the normal cycle. It would seem that the first two cycles are almost certainly anovulatory; the third, in spite of the low (but definite) gonadotropin peak, is ovulatory.

In summary, accepting the given definition of normal patterns of hormone excretion, these were normal for *L. W.* throughout the study with one exception, the gonadotropin pattern in the fourth cycle. The gonadotropin excretion levels in *M. H.*'s fourth cycle varied from the assumed normal as did the body temperature. For *R. S.* the body temperature curve was irregular, the vaginal response reflected a weak to normal estrogen production and a low progestin secretion. For *M. V.*, the data for the fifth cycle show irregularity in gonadotropin excretion, but otherwise all of the available data follow the normal pattern. The first two cycles of *B. W.* were presumably anovulatory, although the body temperature curve is normal; the third cycle was apparently normal, although the gonadotropin output was low. This may have been a case of post-pregnancy irregularity in the re-establishment of a normal cycle.

On the basis of the evidence in these few cases it is not possible to establish types of hormone excretion curves. There is no evidence for an influence of age, either on the regularity of cyclic changes or on the amount of hormone produced, the age range being from 22 to 43 years. Nor did the record of subjective experience provide a basis for an explanation of the irregularities or the differences between subjects which figure 1 portrays.

Quantitative results (fig. 2–5). The positive gonadotropin responses are shown in figure 2. The precipitate was divided and assayed at a dose equivalent to the amount in 3 hours' excretion of urine per rat, using 4 rats (fig. 1). In cases in which there was a positive response (a response was considered positive if the average uterine weight exceeded 50 mg., which is twice the normal weight) the dose was halved and the assay repeated. If the results of this assay were positive, it was considered that there were 16 R.U. of gonadotropin per 24 hours; if negative, that there were 8 R.U. This technic is used, since beyond an optimum dosage there is a diminished uterine response. Thus, with one preparation, a dose equivalent to 3 hours' excretion of urine, the uteri may weigh 120 mg. while with the same amount of another preparation the uteri will weight 100 mg. although the second preparation may contain twice as much (or more) gonadotropin. The gonadotropin determinations in those cycles marked *X* in figure 2 were repeated; all samples for which the response was negative to a dosage equivalent to 3 hours' excretion of urine were re-injected at double the dose. When a response was positive to this doubled dose it was considered that 4 R.U. of gonadotropin was present. The values in R.U. are equivalent to those obtained with similar doses of international standard chorionic gonadotropin.

Estrogens. The results of the assays are shown in figure 1 and are based on the same dosage, which was equivalent to 1 hour's excretion of urine per rat. In some cycles more extensive assays on two dosage levels were made, 12 to 18 rats being used (fig. 3). The results of these assays are given in I.U., the sensitivity of the colony frequently being checked against the crystalline international standard material. This accounts for the slight differences in shape between the curves of figure 3 as compared with the corresponding curves in figure 1.

Pregnanediol. The results of pregnanediol determinations by the methods of Venning and of Astwood, as applied to the same specimens of urine, are shown in figure 4. For these studies, 48-hour urine samples were used. Astwood's method yields pregnanediol, which is calculated as the glycuronidate. Reasonably good agreement between the two methods is shown in two cycles, but not in the other two. We experienced considerable difficulty, as apparently other workers have, in obtaining pure products. We do not consider either method as very satisfactory and the results shown cannot be considered as more than roughly quantitative.

Summarizing the results included in figures 2, 3 and 4 the total gonadotropin output varies greatly from one cycle to another, even in the same subject. For most cycles, the peak is equivalent to 16 I.U. per day. In two cases (*M. H.*, cycle 4 and *M. V.*, cycle 5) amounts equally great were excreted over a period of several days in the early stages of the cycle. The largest total amount per cycle excreted (*M. H.*, cycle 4) was approximately 150 I.U., the smallest demonstrated amount (*B. W.*, cycle 3) was 4 I.U. The maximum peak excretion of total estrogen was approximately 1000 I.U. per day, the usual peak somewhat less. For a complete cycle, the total output usually varied from 5000 to 10,000 I.U. The very low levels of estrogen observed in *B. W.*'s first and second

cycles may represent a condition in non-ovulatory cycles. The peak excretion of estrone was approximately 900 I.U. and of estriol, 400 I.U. Pregnanediol glycuronidate excretion reached a maximum of 11 mg. per day in one case (*M. V.*, cycle 2) but was usually between 5 and 8 mg. The total amount excreted in any one cycle was 86.0 mg., the average being around 50 mg. This compares well with values in other reports.

Validity as ovulation tests. There was a peak in gonadotropin excretion in the mid-interval of 18 of a total of 20 cycles. The range of the days on which the mid-interval peak occurred was narrow, one being found on the 13th day, 8 on the 14th, 6 on the 15th, and 3 on the 16th day preceding the onset of menstruation. Four additional peaks of equal height occurred in these 18 cycles. One such peak preceded menstruation, 2 followed menstruation and one occurred 5 days after the mid-interval peak. The two negative cycles (*B. W.*, cycle 1 and cycle 2) were probably anovulatory, judging from corroboratory evidence.

The bimodal curve, recognized as typical for estrogen excretion in normal women, appeared in all 16 cycles in which estrogen assays were made. The curves were irregular, excretion falling to zero in some cases; in others excretion was continuous. Excretion levels for estrone and estriol, determined separately, appear to follow the same pattern, the latter at a lower level and somewhat later than estrone.

Pregnanediol excretion was regular in the 11 cycles in which it was determined. In no case could it be found in the first half of the cycle; once it appeared, its excretion was continuous until a few days before the next menstruation. In most cases a fairly well defined peak occurred, although the shape of the curve was not uniform.

The phasic changes in vaginal smears followed the sequence described by Rubenstein and others. The day-to-day changes were so gradual, however, that we were never able to select a certain day as sufficiently distinctive to indicate ovulation. Of the 19 cycles studied in this way, 14 could be considered typical; in 3 (*R. S.*, cycles 2 to 4) proliferation was not pronounced and in 2 (*B. W.*, cycles 1 and 2) there were no phasic changes.

Although the body temperature data show a general uniformity, in that the temperature was low at the beginning of a cycle and rose during the cycle, there was a considerable amount of irregularity in this rise. Of the 16 cycles studied, only 6 (*L. W.*, cycles 1 to 4; *B. W.*, cycles 1 and 2) show the sharp rise in the mid-interval which Rubenstein (6, 3rd graph, p. 852) considers typical of the normal ovulative cycle; *B. W.*, however, on the basis of other tests, probably did not ovulate in cycles 1 and 2. In the other 10 there were *a*) distinct rises, in some occurring very early during the cycle (*M. H.*, cycles 1 and 2); *b*) only slight rises (*M. H.*, cycles 3 and 4) or *c*) inexplicable curves (*R. S.*, cycles 1 to 4).

Little has been said so far concerning the subjective experiences recorded by these subjects. All are intelligent women and they made careful observations during the interval. The occasional headaches, colds, periods of ill or well-being and dates of coitus for each subject seemed of little significance. *Subject M. H.* experienced slight intermenstrual bleeding and slight pain during the first two cycles, 2 days before the appearance of the excretion peak for gonadotropin but none during the last two cycles. *Subject L. W.* had attacks of headache, centering on the right side, which occasionally coincided with the presumed time of ovulation, but which occurred at other times as well. *Subject R. S.* had a respiratory infection during the first cycle, which may account for the high temperature noted then. The instances of high gonadotropin excretion at times other than the mid-interval could not be related to the incidence of coitus. In short, no subject was able to record a happening involving the physical, emotional or sex life, which could be related to the other data obtained in this study.

Which methods have their validity confirmed by synchronous occurrence of other positive reactions? The method of 'subjective experience' may be discarded. The body temperature method does not appear to be confirmatory as its record indicates ovulation in cycles 1 and 2 of *B. W.*, although other tests during these cycles indicate that they were ovulative.

The hormonal studies and vaginal smear studies remain to be evaluated. The results of all cycles in which estrogen, pregnanediol and vaginal smear tests were studied confirm each other (estrin plus vaginal smears, 14 cycles;

pregnanediol and vaginal smears, 10 cycles; all three tests, 7 cycles). The appearance of demonstrable amounts of estrin in the urine coincides quite uniformly with the appearance of a cell picture representative of the preovulatory phase and the peak of desquamation agrees reasonably well with the peak of pregnanediol excretion. Finally, the gonadotropin peak invariably follows soon after the rise in estrogen excretion and is, in turn, invariably followed within a few days, by the appearance of pregnanediol. The appearance of high peaks of gonadotropin excretion at other times in the cycle is not associated with simultaneous changes in the results of other tests and so does not seem to indicate multiple ovulation (*M. H.* 4th cycle; *R. S.*, 2nd cycle; *M. V.*, 1st, 2nd and 5th cycles). Although the gonadotropin output in the 3rd cycle of *B. W.* was small, a peak occurred (fig. 2) which was apparently sufficient to bring about ovulation.

The time relationship between the excretion peaks for estrogen and gonadotropin, namely that the former precedes the latter, has again been found to hold. On the basis of this time relationship, a tentative explanation of the mechanism of ovulation has been suggested (2). This has been denied by Werner (11) who found no such constant relationship. He, however, used 48-hour urine samples, which may have obscured the result as the estrogen rise precedes the gonadotropin peak by 1 or 2 days. Our own results have been entirely consistent in this regard.

It seems unlikely that the synchrony in the events described is a mere coincidence. On the basis of present physiologic knowledge the results of 4 tests, gonadotropin excretion, estrogen excretion, pregnanediol excretion and the vaginal response are related to each other and to ovulation. A cycle may be considered to have been ovulatory if marked by *a*) a gonadotropin peak in the mid-interval, *b*) a bimodal wave of estrogen excretion, *c*) pregnanediol excretion during the second half of the cycle and *d*) phasic changes in the vaginal mucosa. Conclusions as to the exact day on which ovulation occurred are less definite, but it seems reasonable to assume that the gonadotropin peak is so closely associated with the phenomenon of ovulation that it may be accepted as indicative of its actual occurrence. It is preceded by the appearance of a peak in estrogen excretion and followed within a few days by the excretion of pregnanediol. The time of the appearance of the gonadotropin peak agrees well with the theoretical time of ovulation as determined by direct studies. At the present time, and on the basis of present evidence, the mid-interval gonadotropin peak appears to us to be the most valid of the indirect methods for the determination of the time of ovulation.

SUMMARY

Twenty menstrual cycles of 5 subjects were studied, using concurrently, from 4 to 6 of the following methods: gonadotropin assay, estrogen assay, pregnanediol determination, vaginal smears, body temperature and subjective experiences. The purpose was to evaluate the validity of these tests on the basis of uniformity in the occurrence of positive responses and synchrony of their appearance. It was concluded that *a*) subjective experiences were valueless as tests for ovulation; *b*), body temperature fluctuations were not sufficiently regular or clear-cut to be reliable; *c*), the uniformity of the results of hormonal assays and vaginal smear confirmed the validity of each and that a certain sequency of events appears typical of the normal cycle; *d*), because of its sharpness and its apparent close association with ovulation, the gonadotropin peak occurring in the mid-interval was considered as most indicative of the exact time of ovulation.

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COMMUNICATIONS

EFFECT OF STORAGE ON URINARY ANDROGENS*

During the past four years we have assayed biologically the androgenic activity of the extracts of over 250 specimens of urine. In many instances the determinations were made on successive daily specimens of urine collected for periods as long as 30 days[1,2,3]. Each extract was assayed on 5 capons and the capons were rested for 3 weeks after the application of an active substance to the comb. Manifestly it has not been possible to maintain a colony of capons sufficiently large to assay each extract immediately after preparation. The only alternative was storage of the extracts. The thick dark red oil, representing the neutral steroid fraction, separated by the technique of Koch,[4] was placed in wide-mouthed glass specimen bottles and the cork sealed with paraffin. No attempt was made to remove the contained air or to replace it with nitrogen. Duplicate assays were made at varying periods of time. This bioassay is reproducible to within only 20 per cent and a difference of twice that magnitude might appear between two unchanged specimens. It is hoped that the data in table 1 may be found useful to other investigators in this field

Table 1. Effect of storage on urinary androgenic activity

Specimen Number	Interval between Preparation and 1st Assay, weeks	Initial Value μg./0.2 cc.	Interval between 1st and 2nd Assay, weeks	Final Value μg./0.2 cc.	Percentage Difference
1	<1	5.0	4	4.2	−16
2	<1	5.0	8	5.0	0
3	<1	5.0	12	5.4	+ 8
4	<1	5.0	12	3.0	−40
5	<1	5.0	16	5.0	0
6	16	3.8	4	3.6	− 5
7	16	4.2	4	3.6	−14
8	16	4.0	4	4.4	+10
9	16	3.3	4	3.4	+ 3
10	16	3.5	16	3.2	− 9
11	16	3.0	24	3.7	+23
12	16	3.8	24	4.0	+ 5
13	16	3.7	28	2.7	−27
14	16	4.2	32	3.8	−10
15	16	2.1	40	1.9	−10
16	16	2.0	40	1.8	−10

It would appear therefore that there is no significant loss of the androgenic activity of the neutral steroid fraction of urinary extracts for periods as long as 10 months when stored in glass vessels with paraffinized corks.

Mary L. Miller, Ph.D.

Department of Pathology
Washington University School of Medicine
St. Louis, Missouri

* This investigation was supported by a grant from the Josiah Macy Junior Foundation.

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EDITORIALS

B VITAMINS AND HYPERTHYROIDISM

HIMWICH, Goldfarb and Cowgill[1] showed that dogs receiving a yeast-free diet developed anorexia in 34 days on the average as compared with 17 days for dogs receiving the same diet plus desiccated thyroid. Drill and Shaffer[2] confirmed this finding. They have observed that when yeast is removed from the diet of a hyperthyroid dog, there is a rapid fall in caloric intake and loss of weight. Injections of vitamin B_1 will increase the caloric intake in such dogs to their previous hyperthyroid level but the dogs will not gain weight until a rich source of vitamin B_2 complex is also supplied. Neither is adequate in itself. By administering a sufficient quantity of B vitamins it was possible for them to maintain the caloric intake and weight of 3 of 4 hyperthyroid dogs for as long as 112 days. In rats, it was found that the active components in the B_2 complex were vitamin B_6 and pantothenic acid.[3]

These observations suggest that vitamin B_1 and the vitamin B_2 complex are related to the caloric intake and maintenance of weight in experimental hyperthyroidism. Drill and Shaffer refer to the observations of Sure[4] and Sherman[5] that the diet of the average American is becoming deficient in the B vitamins. They suggest that this deficiency would be deleterious in patients with toxic goiter and recommend that a larger amount of B vitamins be supplied to such patients in order to maintain food intake and control any loss of weight. Frazier and Ravdin[6] found that 72 per cent of patients with toxic goiter receiving vitamin B_1 and yeast gained weight, whereas only 28.5 per cent of those not receiving supplements of the B vitamins gained weight. This is not a new idea. A few years ago Means, Hertz and Lerman[7] suggested that the diet of patients with toxic goiter be supplemented with vitamin B_1 in the form of Harris yeast powder.

The notion that generous additions of vitamin B_1 and the vitamin B_2 complex might be of value in the treatment of toxic goiter is an interesting one and deserves serious consideration. Drill and Shaffer have, perhaps, attempted to apply their experimental results in animals too literally to the clinic. Thompson, Taylor, Meyer and McNealy[8] have been interested in the preoperative treatment of patients with toxic goiter and have come to the conclusion that gain in weight is more important than any other factor in determining the outcome of operation. They have noted, moreover, that nearly all patients with toxic goiter can be made to gain weight if supplied with an adequate number of calories. In their work no attention was paid to the amount of B vitamins in the diet and it can be said, without qualification, that as long as the diet is well balanced and adequate in calories, its vitamin content may be ignored. However, in the light of the work of Himwich, Goldfarb and Cowgill and of Drill and Shaffer, it would be well to consider carefully the value of the B vitamins in the treatment of patients with toxic goiter who have the disease in a severe form, including those with anorexia and extreme weakness.

W.O.T.

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SIMILARITIES BETWEEN THE ACTIONS OF THE VITAMINS AND HORMONES

THE VITAMINS and hormones have in common many physiologic and pharmacologic properties so that one is forced to conclude that the fundamental reactions of these two groups of substances in the organism may be identical. This point of view is of more than academic interest, for our knowledge of the rôle played by the vitamins in the animal economy in some instances is well established. On the other hand, this knowledge in the case of the hormones is lacking. If it could be demonstrated that the hormones manifest their activity by reactions which are analogous to those of the vitamins one would be justified in drawing conclusions which are of importance in establishing certain fundamental concepts in endocrinology.

The outstanding difference between the vitamins and hormones is the fact that the former are exogenous in origin, the latter endogenous. In other respects the similarity between the two is so striking as to suggest that the vitamins be considered as exogenous hormones, and the hormones as endogenous vitamins. The other obvious difference between the two is the fact that the vitamins are, in general, chemically more stable and more simple compounds than the hormones. This would of necessity have to be so in the case of the vitamins, for otherwise they would be destroyed in the gastrointestinal tract. The hormones, on the other hand, are for the most part unstable compounds or protein-like substances which are ineffective when ingested. This difference in the chemical nature of the vitamins and hormones has suggested that the latter may have resulted as an adaptation on the part of the organism to procure for the body such vitamin-like essentials as either do not occur at all times in the food (as, for example, iodine) or are not available by the usual alimentary route.

A point in common between the vitamins and hormones which sets them apart from the common aliments is the minute dosages of both which suffice to maintain the organism in normal health. The amounts of either of these classes of substances utilized daily is measurable in terms of milligrams, and sometimes in terms of micrograms. This small requirement is readily explicable on the basis that the vitamins and hormones act in the organism as enzymes, that is, as organic catalysts. That this is true in the case of certain of the vitamins has been demonstrated. Thus nicotinic acid, thiamine and riboflavin are established as constituents of several enzyme systems, while ascorbic acid is involved in oxidation-reduction processes. It has not been demonstrated as yet that any of the hormones are involved in an enzyme system similar to those demonstrated in the case of the vitamins. However, the close analogy between the amounts of each used in the organism, and the evidence that each subserves some fundamental process in the body economy, favors the view that the hormones play a rôle similar to that of the vitamins as part of an enzymic system.

One usually thinks of avitaminotic and hormonal disturbances in terms of some outstanding single disorder, for example, of the beri-beri heart or the tetany of hypoparathyroidism. As knowledge of these disorders advances it soon becomes clear that neither a vitamin deficiency nor an endocrine disturbance causes a disturbance in a single bodily function or in only one group of tissues. Insulin, for example, is no longer looked upon as being essential for the utilization of carbohydrate. Even in the diabetic, glucose may be utilized and it is only our ability to detect the presence of abnormal amounts of sugar in blood and urine which has emphasized this aspect of insulin deficiency. The metabolism of proteins, fats, sterols, salt and water are also disturbed, as well as that of the carbohydrates, and the results of these disturbances are reflected in pathologic changes occurring in all the organs of the body. This general involvement to a variable, but nevertheless detectable, extent is found in all vitamin deficiencies and in all endocrine disorders. The individual disorders differ only in the degree and manner in which the sundry physiologic mechanisms are affected and in the extent to which the pathologic changes in various organs and tissues are manifested. This influence of the vitamins and hormones on the body tissues generally indicates that they are involved in some basic chemical reaction of the nature of an enzymatic process, and explains the diversity of defects observed in avitaminoses and endocrinopathies.

Acceptance of the thesis that the hormones act like the vitamins in the organism, and that their action is based on their taking part in some basic enzymic process necessitates reorientation of several time-honored views. The idea that each

hormone subserves a single function is certainly no longer tenable. The view that their action is limited to only one or a few tissues must also be relegated to the past. Even in the case of the so called 'sex hormones,' the available evidence suffices to show that these do not limit their action to the reproductive organs, but also exert demonstrable effects on the heart, circulatory system, skin and muscles. This general action in the organism does not exclude the endocrine glands themselves, for any endocrine abnormality influences the function of the other endocrine glands to some extent. It is not only the hypophysis which controls the endocrine system but each individual endocrine, to some extent at least, is essential for the normal function of the others. In this respect every endocrine disorder is more or less a 'pluriglandular' disorder.[1]

Until investigation reveals the exact chemical function of the hormones in their basic enzymatic action, attempts to define their function must be futile. This has been demonstrated amply by past experience. At present we can say nothing regarding the exact mechanism of action of any of the hormones. We can only define their action in terms of observable defects in their absence or presence in excess. We can not say that the adrenal cortical hormone controls 'permeability,' 'osmotic forces,' or 'sugar or salt metabolism,' but only that these are abnormal in the absence of the normal concentration of the hormone in the body. The thyroid hormone may not necessarily be directly involved in oxidative processes, although its absence results in a decrease in the rate of oxidation and its presence in excess does stimulate an abnormal utilization of oxygen. The mechanism whereby this is accomplished remains, however, unknown.

Acceptance of the view that the hormones act like the vitamins as components of basic reactions will broaden one's view of the science of endocrinology and avoid the narrow and anthropomorphic concepts so prevalent in the past.

A.G.

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A SPECIFIC ENDOCRINE ACTION OF YOHIMBINE

YOHIMBINE ($C_{22}H_{30}N_2O_4$), an alkaloid derived from the bark of the West African yohimbehe tree (*Apocynaceae*), does not have an impressive or enviable therapeutic record. Its chief usage in the past has been that of an aphrodisiac; its promoted indications have been listed as being 'sexual neurasthenia' and impotence in the male and sterility, menstrual irregularities and genital underdevelopment in the female. Goodman and Gilman[1] place yohimbine and its diastereoisomer, corynanthine, in the group of drugs which, like ergotamine and ergotoxine, inhibit the responses of sympathetically innervated structures. They note that, despite its former use in hypertension and its promotion as an aphrodisiac, yohimbine has no valid therapeutic uses at the present time.

The aphrodisiac action of yohimbine has been related, usually, to its production of pelvic and genital hyperemia. Studies of the effects of this drug in experimental animals have led to the general assumption that the estrus which is produced in the rodent is due to pelvic congestion rather than to any specific alterations in the functions of the endocrine system. Clinical observations have described a sensation of heat and tension in the testes and scrotum following the administration of yohimbine. Erections are said to result. No stimulation of spermatogenesis is thought to be produced by yohimbine.

That yohimbine and its hydrochloride continue to be used to some extent for their aphrodisiac effects is indicated by reference to the preparations, listed by the Modern Drug Encyclopedia,[2] which contain these singly or in combinations with other substances. Yohimbine is a common constituent of so-called 'shot-gun' aphrodisiac preparations which often contain an imposing number of ingredients: extract of nux vomica (or strychnin), desiccated thyroid, pituitary and suprarenal glands and, depending upon the sex of the patient to be treated, desiccated testis or ovarian residue and corpus luteum.

The possibility that yohimbine might exert a specific action on the endocrine system appeared in Shen's[3] studies. A number of drugs including nicotine and yohimbine were found to produce marked dispersion of the melanosomes of frogs, providing the pituitary was intact. Expansion of

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the melanosomes failed to occur in hypophysectomized animals.

In the November issue of *Endocrinology* Fugo and Gross[4] of the Department of Pharmacology of the State University of Iowa have submitted clear-cut proof that yohimbine's induction of estrus in the rat is not due to hyperemia but rather to a specific stimulation of the anterior lobe of the pituitary gland.

These authors' studies and findings are summarized briefly.

Adult female rats were treated with yohimbine hydrochloride for periods which ranged from 40 to 101 days and with daily doses which ranged from 1 to 4 mg. Those animals which received the lower doses (1 and 2 mg.) experienced episodes of prolonged estrus while those animals given the higher doses (3 and 4 mg.) developed a condition which resembled pseudopregnancy.

Chronic treatment of adult castrated rats with the drug produced no cornification of the vaginal epithelium. This was proof that the prolonged estrus observed in the normal rats was not the result of hyperemia.

The facts that yohimbine required the pituitary gland for its action and that it did not act directly upon the ovaries were established by the observation that no estrus followed treatment of hypophysectomized rats with this drug.

Immature ovaries devoid of corpora lutea were implanted into the anterior chamber of the eyes of adult normal and castrated male rats. Treatment of these animals with yohimbine hydrochloride produced normal corpora lutea in these imlanted ovaries. This observation established the fact that the pituitary of the male rat could be caused to release the luteinizing principle, an observation not previously made.

Daily injection of 1 mg. of yohimbine hydrochloride into immature female rats produced no estrous phenomena. The likely explanation, apparently, is that the prepubertal pituitary of this animal is structurally incapable of stimulation.

The authors conclude that the results reported present evidence that the alkaloid, yohimbine, stimulates the anterior lobe of the pituitary causing it to release excessive amounts of its principles, especially the luteinizing principle.

Prior to these studies of Fugo and Gross, there was no clear-cut evidence that pituitary function could be stimulated by non-endocrine pharmacodynamic agents. The fact is accepted generally that moderate doses of estrogens are capable of increasing the rate of discharge of the luteinizing gonadotropin from the rat's pituitary. Some evidence also exists that cortical steroids may increase the discharge of follicle-stimulating gonadotropin by the pituitary. Yohimbine, however, by virtue of its pituitariotropic action is capable of releasing luteinizing gonadotropin from the pituitary of the male rat, an effect which estrogens do not produce.

These studies will result, doubtlessly, in a revamping of our concepts of yohimbine. A new implement is provided for further explorations of gonado-pituitary reciprocities. We shall await still further experimental studies with yohimbine, particularly those upon the monkey, an animal which has had such a good score in furnishing genesiologic data translatable to the human species.

The clinical possibilities of a pharmacologic agent with the pituitary-stimulating properties proven for yohimbine, in the rat, are manifold. Such an agent offers the hope of stimulative rather than replacement therapy in many of the hypofunctional conditions of the pituitary. There should be, however, no premature therapeutic excursions. There is experimental ground work to be done. The relationship between the specific pituitary-stimulating dose and the toxic dose must be established. Various toxic effects have been described after large or frequently repeated doses of yohimbine, including vertigo, salivation, sweating, gastric disturbances; a delirium similar to that of acute alcoholism has followed large doses. Despite the fact that it has been used in the past to lower high blood pressure, yohimbine may produce further elevations and, thereby, may cause vascular accidents.

Assuming that the larger doses, i.e., one-half grain thrice daily, recommended for some of the proprietary preparations of yohimbine do not cause toxicologic effects, if given repeatedly, a daily clinical dosage of 100 mg. may be possible; this may be compared with the daily doses of 1 to 2 mg. found effective in the rat. The ratio of these doses is not out of proportion to some of those used in gonadotropic therapy, i.e., 50 to 100 rat units.

One is safe in predicting that these studies of Fugo and Gross will stimulate and inspire additional investigations. The end result of these may be the eventual assignment of a more respectable and important therapeutic rôle to the alkaloid of yohimbehe bark.

E.C.H.

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LETTERS

UTERINE BLEEDING

To the Editor:

In the Journal of Clinical Endocrinology, November, 1942 I read with interest Dr. Robert B. Greenblatt's paper on 'Observations on the Mechanism of Uterine Bleeding.'[1]

Dr. Greenblatt refers to the paper of Bartelmez.[2] In commenting on this paper he states 'this case study, on the basis of proven insufficiency of the endometrium, further emphasizes and confirms the observations of Bartelmez that the myometrium and its vascular supply are dependent upon endocrine control and are responsible for uterine bleeding. Bartelmez believes that the explanation for the reduction or stoppage of the flow of blood to the mucosa must be sought for in the myometrium and not in the endometrium.

We have now taken more than 8000 endometrial biopsies 1 to 7 days before the expected menstrual period, in the first 24 hours of the period, and during the actual flow of normal and abnormal uterine bleeding and have never observed any cases similar to his. We have also produced bleeding such as Dr. Greenblatt describes, and on removing the uterus, have always found endometrium.

Dr. Greenblatt's reference is to an article which states 'so far as the mechanism which brings about bleeding is concerned it would appear from what has been said that the question can be narrowed down to the factors which control the coiled arteries of the endometrium.' He concludes that the myometrium is more important than the endometrium. Yet, if he remembers, this same article discussed endometrial implants into the eyes of monkeys. There was no myometrium in these experiments so one could conclude that the myometrium plays no part in menstruation or abnormal uterine bleeding.

Our work[3] tends to show that normal and abnormal uterine bleeding are dependent upon the level of estrogen in the blood and to the spiral arteries of the endometrium

Karl John Karnaky, M.D.

1215 Walker Street
Houston, Texas

[1] Greenblatt, R. B.: Observations on the mechanism of uterine bleeding. *J. Clinical Endocrinology* 2: 645. 1942.

[2] Bartelmez, G. W.: Glandular physiology and therapy. Menstruation. *J. Am. Med. Assoc.* 116: 702. 1941.

[3] Karnaky, K. J.: Cause of menstruation and uterine bleeding. *South. M. J.* 33: 1285. 1940.

CARDIOTOXIC GOITER

To the Editor:

In a recent issue of *Endocrinology*, Schmidt and Hertzler[1] have published an article, "Cardiotoxic Goiter—A Distinct Entity." These authors suggest that there is produced in the goitrous thyroid a substance which increases the heart rate without affecting the rate of metabolism. They speak of 'chronic hyperthyroidism with normal metabolic rate.' The notion that the diseased thyroid may produce an abnormal product has always been an intriguing one, but up to the present time, no good evidence I think has been presented in support of the hypothesis. In our experience, the only patients with non-toxic goiters who have presented cardiac symptoms have been those with independent heart disease. In a few cases we have observed patients with definite clinical evidence of exophthalmic goiter, but a rate of metabolism within the limits of normal. In such patients, not infrequently the administration of iodine will cause the basal metabolism to drop to a slightly subnormal level in association with clinical improvement. This observation would suggest that for these particular patients, the slightly low level of metabolism is in reality a normal one.

Observations with diiodotyrosine, desiodothyroxine and diiodothyronine do not lend support to the hypothesis that an abnormal product is produced in toxic goiter. While the hypothesis presented by Schmidt and Hertzler is an interesting one, we do not feel that they have collected adequate evidence for its support.

W. O. Thompson

University of Illinois
College of Medicine
Chicago, Illinois

[1] Schmidt, C. R., and A. E. Hertzler: *Endocrinology* 31: 684. 1942.

ENDOCRINOPATHIES IN THE MILITARY SERVICE

To the Editor:

Examination of the civilian entering military service presents many difficulties which the physicians who are doing the actual work fully appreciate. For that reason the surprising thing is not that certain medical conditions are missed, but that more are not missed. In military hospitals, when such cases are discovered and more particularly when several happen to present themselves in succession, a distorted impression is apt to prevail and a critical attitude toward preliminary examinations be taken. In military hospitals the patient can be studied at leisure since he can be hospitalized for 14 days to 4 months; in contrast, the preliminary examination takes but a few minutes. The inference is obvious. Furthermore, many unacceptable conditions which are present prior to induction may have been in the incipient stage at that time and hence obscure; a few months later the characteristics may have progressed to the point that they are obvious even to a layman. All of these factors must be taken into consideration before critical judgment is pronounced.

A survey of the records here has been made in order to see what endocrinopathies are present. Since the opening of the Lawson General Hospital, July 22, 1941 to August 31, 1942, 6197 patients have been admitted. How large an Army these patients came from is impossible to estimate but we do know that the military population of the 4th Service Command is extensive. Of the 6197 admissions a certain percentage were discharged from the Army because of a medical disability, being given a Certificate of Disability Discharge (CDD). The figures given below are based on these CDD proceedings, i.e. they refer to those soldiers who appeared before a Board and were discharged from service. All who had endocrinopathies were naturally discharged so that these figures are quite accurate. Thus of 6197 admissions, 1215 appeared before the CDD board and of these 34 were classified as endocrinopathies. From this figure it will be seen that soldiers discharged from the service with endocrine defects comprise 2.7 per cent. Classification of these endocrinopathies is shown below.

Diabetes mellitus	26
Hypopituitary disease	3
Colloidal goiter	1
Exophthalmic goiter	2
Diabetes insipidus	1
Addison's disease	1
Total	34

The incidence of endocrinopathy is therefore very small in this Army General Hospital. In this group the incidence of diabetes is the highest. I do not see how, without extensive laboratory work, the prediabetis could have been diagnosed. I think we can feel confident that on the whole the local medical examining boards are rendering satisfactory service.

Henry J. John,
Lt. Col. M. C.

Lawson General Hospital
Atlanta, Georgia

Abstracts of
CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. *Collaborators:* ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, R. B. GREENBLATT, E. C. HAMBLEN, R. G. HOSKINS, J. E. HOWARD, J. P. PRATT, J. T. LEWIS, A. E. MEYER, C. A. PFEIFFER, BORIS B. RUBENSTEIN, EMMERICH VON HAAM.

ENDOCRINE GENERAL

ANONYMOUS.

Endocrine factors in acne vulgaris. *Brit. M. J.* (4254): 75. 1942.

An epitome of the contradictory opinions which are held in regard to the etiology of acne. The majority of articles dealing with endocrine therapy deal with fewer than 10 cases, usually without any control series. The uncritical nature of many reports is no credit to clinical investigation. The only real argument in favor of endocrine etiology is the regularity of its appearance at puberty and its ebb and flow with the menses.—*J. B. Paton* (*Biol. Abst.*).

ARNELL, R. E., AND P. L. GETZOFF.

Renal and ureteral calculi in pregnancy. *Am. J. Obst. & Gynec.* 44: 34. 1942.

From the study of records of 46,333 female patients admitted to Charity Hospital during a period of 18 months, it was found that the incidence of renal and ureteral calculi was 1:1100 non-pregnant women. During the same time of 9,882 women admitted to the obstetric service 12 had calculi, an incidence of 1/820. Factors in the formation of stones are listed as including race, sex, endocrine conditions, errors of vitamin and mineral metabolism but the chief causes apparently are stasis and infection.—*E.C.H.*

BARNES, JOSEPHINE.

Inhibition of lactation by synthetic estrogenic substances; with special reference to dienoestrol. *Brit. M. J.* 1: 601, 1942.

The effect of "dienoestrol" ($\gamma\delta$-di-p-hydroxyphenyl-$\Delta^{\delta\delta}$-hexadiene) was compared with that of stilbestrol and hexestrol on the inhibition of lactation in 134 patients. A total dose of 30 mg. of stilbestrol over 5 days was usually effective in inhibiting lactation without unpleasant breast symptoms but more uniform success was obtained with larger doses. Much smaller doses of dienoestrol (1 to 5 mg. in 5 days) were given and the results were distinctly inferior; in only 15 out of 37 cases was lactation satisfactorily controlled. This treatment was most effective when initiated immediately after parturition.—*E.B.A.*

BEASER, S. B., AND T. B. MASSELL.

Therapeutic evaluation of testosterone in peripheral vascular disease. *New England J. Med.* 227: 43. 1942.

Six men between the ages of 45 and 62 and suffering from intermittent clandication were given intramuscular injections of testosterone propionate three times weekly for periods of from 6 weeks to 6 months in a dosage of from 30 to 225 mg. per week. One patient exhibited subjective evidence of slight improvement when the dose was increased to 225 mg. per week, but no evidence of improvement, as judged by a walking test, could be found in the other 5 patients.—*E.B.A.*

BEHRENDT, H.

Studies on blood phosphorus. II. Blood phosphorus partition in tetany and guanidine poisoning. *Amer. J. Dis. Child.* 64: 475. 1942.

The concentration of organic ester phosphorus in the blood was found normal or decreased by the Lohmann and Vissen method in a nine-year-old boy with chronic tetany. The organic ester phosphorus and the total phosphorus were decreased and the muscular total phosphorus in experimental guanidine poisoning in two rabbits.—*M.B.G.*

BENNETT, H. G., JR.

Methods for the evaluation of estrogen therapy in the menopause. *Am. J. Obst. & Gynec.* 44: 296. 1942.

Three hundred and twenty-four urinary estrogen assays of 80 climacteric patients, 289 urinary gonadotropin assays of 60 climacteric women, 124 vaginal smears of 62 climacteric women and studies of the cervical mucus of 66 climacteric women were correlated with the pre-treatment and treatment status of the patients.

In general climacteric patients have little if any estrogenic substance in the urine, show atrophic changes in the vaginal smears, have increased amounts of gonadotropic substance in the urine and secrete a scanty, viscid, cellular mucus from the cervical glands. In patients adequately treated with estrogens, the urinary levels of es-

trogens usually rise to levels found in menstrual life, urinary gonadotropin decreases or disappears, the vaginal smear typically changes to an estrous one and the cervix secretes abundant, clear, alkaline, acellular mucus. The asymptomatic patient may show evidence of estrogenic deficiency while the patient with symptoms may give evidence of estrogen activity. It is not believed that the amount of estrogen required to alleviate the vasomotor symptoms of the climacteric is necessarily the amount required to give normal preclimacteric hormone levels as tested by the methods studied.—*E.C.H.*

BICKERS, W.

A study of contractions in labor based on kymographic records obtained from an intrauterine balloon. *Am. J. Obst. & Gynec.* 43: 851. 1942.

Patterns of uterine motility during labor were studied in 22 patients using an extraovular, high fundal, intrauterine balloon connected to a mechanical ink recorder. It was found that labor contractions during the early first stage had a relatively low amplitude superimposed upon moderate tetany. As labor progressed with intact membranes, tetany became more marked. Following rupture of membranes, spontaneous or artificial contractions were characterized by the absence of tetany. The increased amplitude which resulted was considered to augment the expulsive efficiency of each contraction.—*E.C.H.*

BIEREN, R. E., AND B. C. COMPTON.

The estrogenic properties of dihydrostilbestrol (hexestrol). *Am. J. Obst. & Gynec.* 44: 287. 1942.

Clinical applications were made in the therapy of 37 patients with symptoms referred to the climacteric, 8 patients with functional dysmenorrhea and 12 children with gonorrheal vaginitis.

The authors concluded: hexestrol may be substituted for diethylstilbestrol to circumvent nausea and to secure more satisfactory responses in patients 'resistant' to the latter agent. Nausea from hexestrol is milder than that produced by comparable doses of diethylstilbestrol. The effective dose in adults is about ten times that of diethylstilbestrol. In children, however, hexestrol is more effective than diethylstilbestrol in equal doses in the treatment of gonorrheal vaginitis.—*E.C.H.*

BLOTNER, H., AND P. KUNKEL.

Diabetes insipidus and pregnancy; report of two cases. *New England J. Med.* 227: 287. 1942.

In one patient the fluid intake and urine output increased during the 7th month of pregnancy and then steadily declined to near normal; 1 day after delivery polyuria and polydipsia abruptly returned. The second patient developed diabetes insipidus during the 5th month of pregnancy which disappeared after delivery. It is concluded that diabetes insipidus may be intensified, improved or unaltered by pregnancy.—*E.B.A.*

BLUMBERG, A., AND O. BILLIG.

Hormonal influence upon 'puerperal psychosis' and neurotic conditions. *Psychiatric Quart.* 16: 454. 1942.

In pregnancy, intensive hormonal changes take place; the stress of interglandular adjustment of the endocrine system is much increased. If the hormone-producing organs are not able to meet this increase, pathological conditions of some type will supervene. The individual having a potentially psychotic personality makeup is prone to developmental symptoms. Puerperal psychoses apparently do not constitute a specific syndrome, but depend in coloring upon the prepsychotic personality of the patient. The prognosis for mental recovery is good in the delirious type of reaction and in the manic-depressive group. In the schizophrenic reaction type, however, the outlook is far less hopeful; perhaps 20 or less per cent of the patients recover spontaneously. With insulin shock therapy it is undoubtedly possible to increase the incidence of recovery. The authors describe a case in which only partial improvement was obtained with insulin shock, although full recovery was established by combining the insulin treatment with hormone therapy. This patient had developed schizophrenia after the birth of her first child. Exacerbation of the psychotic symptoms occurred during the postovulative phase of menstruation or on the day when menstruation was to be expected but did not actually take place. When the patient became pregnant again, in order to prevent a recurrence of her previous symptoms, she was started on progesterone, 2 mg. twice weekly, beginning with the 5th month of pregnancy. After the delivery, the treatment was continued with weekly injections of 2 mg. for the first 4 weeks. Later 2 mg., twice monthly, were given for another 2 months. The patient's mental condition remained good. Two other cases are also of interest. The first (aged 33) exhibited a mild premenstrual tension. She developed a series of non-malignant breast tumors, one of which was enucleated and the others reduced and controlled by progesterone. The

psychic tension, which had coincided with the physical symptoms, disappeared under progesterone medication given every month. In a 3rd patient, cyclic organic symptoms were linked with a premenstrual tension. Both disappeared on progesterone treatment. The physical anomaly was a cystic right ovary which increased in size during menstruation and just before, and decreased after menstruation. Eventually the ovary, tube and body of the uterus were removed. The other tube and ovary had been removed a number of years previously. Progestin treatment relieved the ensuing return of tension with hot flashes. These 3 patients show a common underlying factor, the premenstrual exacerbation of their symptoms. Both the hormonal change after childbirth, degeneration of placenta (sudden decrease of progesterone level) and exacerbation of psychotic symptoms during the postovulative phase (at a time when progesterone would normally be increased) suggest a disturbed endocrine (probably progesterone) balance. In the first case, insulin treatment produced a marked decrease of the psychotic symptoms and sensitized the autonomic centers (possibly involved in the schizophrenic process) for the following progesterone treatment. Progesterone completed the mental recovery; but when it was discontinued, menstrual irregularity appeared. The authors suggest that experimental determination of the endocrine balance is of great value for the therapeutic approach in schizophrenia.—*Hartford Abstracts* (*R.G.H.*).

BOND, E. D., AND T. D. RIVERS.

Further follow-up results in insulin-shock therapy. *Am. J. Psychiat.* 99: 201. 1942.

One of the first American groups of schizophrenic patients treated by the insulin-shock method was that of Bond and his colleagues at Philadelphia. The immediate recovery rate of 55% in the insulin-treated group was 5 times as high as that of control cases in the same hospital. The higher rate leveled off in subsequent years to about 33%. Except as 3 patients died of shock none of the 188 reported showed signs of brain damage or mental deterioration greater than that of untreated patients. Deaths subsequent to the treatment were of about equal relative frequency in the shock-treated and in the control group. The improvement in the treated patients occurred promptly (in about six weeks) while that in the control groups usually came considerably later.—*R.G.H.*

BOURGEOIS, G. A.

The identification of fetal squamas and the diagnosis of ruptured membranes by vaginal smear. *Am. J. Obst. & Gynec.* 44: 80. 1942.

Rupture of fetal membranes may be diagnosed with good accuracy by studying vaginal smears and identifying the fetal squamas, the characteristics of which are discussed.—*E.C.H.*

BUXTON, C. L.

The use of estrogens in the treatment of leukoplakia, kraurosis and senile vaginitis. *Am. J. Obst. & Gynec.* 44: 109. 1942.

Treatment consisted of the local application of an ointment of lanolin base containing 10 mg. of diethylstilbestrol per 30 cc. of salve. Of this ointment, 30 cc. was applied locally for one week. If itching was relieved, therapy was continued as long as one month. Of 9 patients in the kraurosis-senile vaginitis group treated, 5 were completely relieved of pruritis. Of 7 patients with leukoplakia treated, 2 were completely relieved.—*E.C.H.*

DUCKMAN, S., AND T. R. TURINO.

The use of methyl testosterone for the relief of breast engorgement in the puerperium. *Am. J. Obst. & Gynec.* 44: 112. 1942.

The recommended therapy is the administration of 150 mg. in 5 oral doses of 30 mg. each, every 4 hours, beginning treatment on the 3rd or 4th postpartum day.

Results of treatment of 50 patients were: good in 44, fair in 4 and poor in 2.—*E.C.H.*

EMERY, F. E., C. S. MATTHEWS AND E. L. SCHWABE.

The absorption of stilbestrol and theelin from cysts of sesame and peanut oils. *J. Lab. & Clin. Med.* 27: 622. 1942.

Sesame oil and peanut oil, containing 1.0 mg. of stilbestrol per cc., were injected subcutaneously and intramuscularly in rats. The formation of cysts following these injections was observed in all rats (210) injected intramuscularly and was usually present in rats (50) injected subcutaneously. Oil obtained from the cysts was tested on castrated rats for stilbestrol and theelin. The curves for these tests showed that in some cases all the estrogenic activity was gone by the third day, but in a few rats some stilbestrol remained in the cysts even after twenty days. This is in marked contrast to theelin, in which case the time of retention was reduced to approximately

nine days. These cysts, containing oil, remained in the tissues for many months.

Castrated rats were given 1.0 mg. of stilbestrol or theelin in 1.0 cc. of peanut oil, and the estrous cycles were taken daily. These also confirmed the slow absorption of stilbestrol compared with theelin after a single oil injection.

Oils differ in their ability to form cysts. The present experiments indicate a similarity between sesame oil and peanut oil, judging by their ability to form cysts and by the duration of estrus induced by the stilbestrol remaining in these oil cysts.—*Authors' Abstract.*

FELDMAN, S., J. POLLOCK AND A. R. ABARBANEL.

Treatment of senile pruritus with androgens and estrogens. *Arch. Dermat. & Syph.* 46: 112. 1942.

Sixteen patients suffering from senile pruritis were treated with estrogens and androgens: in 12 uniformly good results were obtained; 4 showed a certain improvement. Extremely small doses were used—10 mg. of testosterone propionate or 1 mg. of estradiol dipropionate, subcutaneously. In 1 case, such dosage failed, but good results were observed with a 20 mg. pellet of testosterone propionate. When senile pruritis in the female was treated with testosterone propionate and in the male with estrogens, no results were obtained; reversal of treatment produced an almost immediate response. This would tend to show that in senile pruritis androgens and estrogens act specifically in the individual sexes.—*I. C. Winter (Biol. Abst.).*

FLEXNER, L. B., AND A. GELLHORN.

The comparative physiology of placental transfer. *Am. J. Obst. & Gynec.* 43: 965. 1942.

The transfer of sodium across the placentas of 6 different laboratory animals at different stages of pregnancy was investigated. Animals (guinea pig, rat, rabbit, cat, goat and sow) were chosen to give at least one representative of each of Grosser's morphologic types of placentas. The rates of transfer of sodium across unit weights of these four types of placentas were found to depend upon the morphologic structure of the placenta: the smaller the number of tissue layers placed between maternal and fetal circulations, the greater was the rate of transfer across a unit weight of placenta. A correlation was found to exist between the supply of sodium transferred to a unit weight of placenta and the rate at which the unit weight of fetus was growing.—*E.C.H.*

FRIEDMAN, M., AND R. FINKLER.

The treatment of sterility with 'small dose' of X-ray therapy. *Am. J. Obst. & Gynec.* 43: 852. 1942.

This is a case report of a patient 26 years of age with irregular uterine bleeding (prolonged at times and infrequent at others) who experienced two pregnancies after receiving one series of 80 r of roentgen therapy to the pituitary and to each ovary and another pregnancy after another similar series of therapy.—*E.C.H.*

GOLDBERGER, M. A., AND R. T. FRANK.

Biologic assay of the estrogens in pregnancy blood. *Am. J. Obst. & Gynec.* 43: 865. 1942.

The estrogenic potency of 86 pregnancy bloods was studied by the 1928 method of these workers (*J.A.M.A.* 90: 376. 1928). Attempts to increase the yield of estrogens by hydrolysis of the blood were unsuccessful. Combined ether and alcohol extraction of the sodium sulfate blood powder was found more effective than ether or alcohol extraction alone.

The greatest concentrations of estrogens were encountered just prior to labor. Estrogen levels increase gradually from the fifth week. These levels do not exceed those of non-pregnant women until the 17th week. The suggestion was made that the estrogens probably circulate in the free state in the blood.—*E.C.H.*

GREENE, R. R., AND S. C. HARRIS.

The percutaneous potency of progesterone. *J. Lab. & Clin. Med.* 27: 746. 1942.

In 37 immature rabbits primed with estrone, the effect of parenteral vs. percutaneous progesterone was tested using the McPhail method for grading progestational responses. In oil as solvent, progesterone is 10 times more effective parenterally than percutaneously. Alcohol as a solvent for percutaneous administration more than doubled the effective potency of the progesterone, but the parenteral route still remained the more effective.—*B.B.R.*

GREENHILL, J. P.

The use and potency of synthetic estrogens. *Am. J. Obs . & Gynec.* 44: 475. 1942.

The effectiveness of three synthetic estrogens, diethylstilbestrol, hexestrol and 118-B, was tested by assay in humans. The subjective response of climacteric women was used as the end

point of this assay. It was found that a satisfactory daily therapeutic dose of diethylstilbestrol is 1 mg., of hexestrol 2.5 to 5 mg., and of 118-B, 1 to 2 mg. Hexestrol was found to be less toxic than diethylstilbestrol and 118-B far less toxic than either hexestrol or diethylstilbestrol.—*E.C.H.*

GRIFFITH, L. S., AND W. P. L. MCBRIDE.

The anovulatory factor in sterility. *Am. J. Obs. & Gynec.* 43: 1012. 1942.

Eight patients, aged 22 to 39 years, were diagnosed as having anovulatory cycles. Six patients were diagnosed upon the basis of single premenstrual biopsies. The other two patients had had respectively six premenstrual biopsies between 1938 and 1940 and several biopsies in the premenstrual interval. Two injections of equine gonadotropin, as a rule, on the 10th to 12th or 12th to 14th days of the cycle, were given. Individual doses ranged from 400 to 800 I.U. Ovulation, upon the basis of premenstrual biopsies (19th to 22nd day of cycle), was judged to have been produced in 7 of the 8 patients.—*E.C.H.*

HALPERT, B.

Intratesticular hemorrhage: a birth trauma. *Am. J. Obs. & Gynec.* 43: 1028. 1942.

Eight cases of intratesticular hemorrhage in association with vertex presentations are described.—*E.C.H.*

HAMAN, J. O.

The length of the menstrual cycle. *Am. J. Obst. & Gynec.* 43: 870. 1942.

An analysis of 2460 calendar records of 150 normal women was made. It was found that the most common cycle was 28 days (15% of all cycles). The average length of all cycles studied was 28.4 days. No instance of absolute regularity was observed. There was no evidence of groupings in multiples of 7, i.e., 21, 28 or 35 day cycles. The distribution of cycle lengths followed the Gaussian curve.—*E.C.H.*

HAMBLEN, E. C., W. K. CUYLER AND M. BAPTIST.

Pregnanediol determinations in gynecology and obstetrics. *Am. J. Obst. & Gynec.* 44: 442. 1941.

Results of a four-year study designed to evaluate Venning's pregnanediol method as a practical and trustworthy aid in the diagnosis of progestin levels in gynecologic and obstetric practice are reported. Data upon quantifications of 2193 twenty-four-hour urines of 102 patients (90 gynecologic and 12 obstetric) are analyzed.

When correlations with studies of endometrial biopsies terminating ovarian cycles investigated by pregnanediol determinations were made, it was found that of 49 patients, whose episodes of bleeding occurred from progestational endometriums, 21, or 42.86 per cent, *excreted no pregnanediol* and that of 16 patients, whose episodes of bleeding occurred from estrogenic bleeding, 10, or 62.5 per cent, *excreted pregnanediol* in amounts of the same order as those excreting it in association with progestational bleeding. Some possible explanations of these variabilities are discussed.

More consistent data were secured on 25 patients who had no bleeding cycles. All of the 7 patients with delayed menarche and all of the 6 patients past menopause excreted no pregnanediol. Three of the 52 patients with intercurrent amenorrhea, however, excreted pregnanediol. The clinical records of these patients suggest the likelihood that these had cyclic ovarian functions.

No consistent relationships were identified between the curve of pregnanediol excretion and the predicated luteal phase of the cycle or between the degree of progestational proliferation of the endometrium and the amount of pregnanediol excreted.

The data upon the 12 obstetric patients were quite consistent. All excreted pregnanediol. The four patients, whose pregnancies progressed to term, despite either histories of recurrent abortions or intercurrent threats to abort, excreted normal amounts of pregnanediol. In 7 of the remaining 8, who aborted and miscarried, studies were continued sufficiently long to be significant. The pregnanediol excretions of these were either initially and continually low or became decreased with some daily values dropping to zero seven to ten days prior to termination of pregnancy. Since these accidents to pregnancies occurred despite intensive progesterone therapy, these data on pregnanediol excretion were of no clinical value in gauging dosage levels.

The following conclusions are held warranted from the foregoing data: 1) Venning's method is unreliable as a diagnostic aid in gynecology; and 2) the data supplied by it in obstetrics at present permit no effective therapeutic endeavors, and while these may be of prognostic import, their belated warnings are often at variance with the prognosis suggested by earlier data.—*E.C.H.*

HARTMAN, C. G.

Contributions of studies on primate animals to gynecologic thought. *Am. J. Obst. & Gynec.* 44: 156. 1942.

The value of experimental data afforded by the monkey in gynecology is described. Some differences between the genesiologic physiology of the monkey and woman are described. These differences are of minor import as compared with major significance of the similarities. This fact gives the monkey a high score as an experimental animal for the gynecologist.—*E.C.H.*

MACBRYDE, C. M., D. CASTRODALE, E. B. HELWIG AND O. BIERBAUM.

Hepatic changes produced by estrone, estradiol and diethylstilbestrol. *J. Am. Med. Assoc.* 118: 1278. 1942.

Large doses of natural estrogens produced fatty and hydropic degeneration in the liver of eleven dogs as shown by positive staining with scarlet red and failure to take Best's carmine stain. Since these changes occurred before the appearance of any hemorrhagic state they were presumably the result of direct action on the liver—*C.P.*

MANN, B., D. R. MERANZE AND L. J. GOLUB.

The histopathologic diagnosis of atypical endometrium. *Am. J. Osbt. & Gynec.* 44: 460. 1942.

The authors advise curettage rather than endometrial biopsy because of variable findings in different areas of the endometrium; they question the validity of correlational studies of endometrial patterns and the hormonal status.—*E.C.H.*

MOORE, R. A., I. BITTENGER, M. L. MILLER AND L. M. HELLMAN.

Abortion in rabbits fed a vitamin K deficient diet. *Am. J. Obst. & Gynec.* 43: 1007. 1942.

It is reported that vitamin K deficiency and hypoprothrombinemia in pregnant rabbits result in abortion at the end of the first trimester of gestation.—*E.C.H.*

PALMER, A.

Cyclical estrogen therapy. *Am. J. Obst. & Gynec.* 44: 56. 1942.

The harmful effects of continuous, as opposed to cyclical, estrogenic therapy of experimental animals and humans are discussed. The general availability of diethylstilbestrol necessitates consideration of these effects. The recommended dosage of diethylstilbestrol in the treatment of climacteric women varies between 0.1 and 0.5 mg. daily by mouth for 21 days, followed by a 5 to 10 days interval without therapy. The recommended dosage of diethylstilbestrol for young women with hypo-ovarian amenorrhea or primary hypogonadism is 1 mg. daily for 7 days followed by 5 mg. daily for 7 days. The withdrawal interval should be 14 days. At least daily, as opposed to less frequent, administration of diethylstilbestrol or other unesterfied estrogens during a cycle of therpay is advised for the purpose of maintaining an excretory and probably a circulatory estrogen level.—*E.C.H.*

REYNOLDS, S. R. M.

Method for correlating data from menstrual cycles of different lengths. *Am. J. Obst. & Gynec.* 44: 155. 5942.

A simple nomogram is described for determining the percentile value of any day of a menstrual cycle by counting back from the onset of the next menstrual period.—*E.C.H.*

ROSENBERG, M., AND S. B. SCHENCK.

Gestation fourteen years after radium induced amenorrhea. *Am. J. Obst. & Gynec.* 43: 1033. 1942.

An enlarged uterus (size of three months' pregnancy) removed from a 47 year old woman who had received 1200 mg./hr. of intrauterine radium therapy 14 years previously proved to contain a normal pregnancy.—*E.C.H.*

SOULE, S. D.

Diethylstilbestrol. *Illinois M. J.* 81: 474. 1942.

Diethylstilbestrol is indicated wherever there is need for estrogenic therapy, since it is active and orally effective. When using dosages as high as 30 to 40 mg. daily the author found toxic effects that disappeared when the dosage was cut to 1 to 2 mg. per day. The smaller dose is an adequate amount of drug with which to anticipate satisfactory estrogenic response. Stilbestrol and thyroid are compatible and when used together adequate results can be obtained with ¼ to ½ mg. daily. A series of 10 individuals who had received continuous treatment at low levels of dosage for 6 months to 2 years is presented together with the results of tests showing the absence of toxicity.—*L. N. Wolf* (*Biol. Abst.*).

SMITH, G. V. S., O. W. SMITH AND S. SCHILLER.

Clinical experiments in relation to the excretion of the estrogens. I. Urinary estrogens before and after the injection of estrone into a patient with surgical menopause. *Am. J. Obst. & Gynec.* 44: 455. 1942.

The patient, aged 50 years, had had supravaginal hysterectomy and bilateral salpingo-oophorectomy done 8 years previously. The 72-hours pretreatment urine specimen contained 90 I.U. of estrogenic activity located in the estradiol fraction. During the 72 hours following the injection of 5 mg. of estrone, 3350 I.U. of estrogens was recovered, 64 per cent as estradiol, 19 per cent as estriol and 17 per cent as estrone. In terms of activity, 6.7 per cent of the injected material found its way into the urine. From this experiment, it is concluded that in the castrated female: estrone is converted in the body both to estradiol and estriol; this conversion mechanism is favored by retardation of steroid degradation; the internal genitalia are not necessary for these processes; less than 3 per cent by weight of injected estrone reaches the urine in recognized forms; hydrolysis with the addition of zinc recovers more of the injected estrogen, this fact being explainable upon the basis of rehydrogenation of inactive products of estrogen oxidation.—*E.C.H.*

SPENCE, A. W.

Sublingual administration of methyl testosterone. *Brit. M. J.* 1: 668. 1942.

In a previously treated eunuch, a comparison was made between the relative effectiveness of methyl testosterone administered orally and by the sublingual route. Maintenance of normal sexual activity followed a daily oral dose of 15 mg. By the sublingual route an equal degree of clinical improvement was obtained with 10 mg. daily. —*E.B.A.*

WATERS, E. G.

Weight studies in pregnancy. *Am. J. Obst. & Gynec.* 43: 826. 1942.

The data upon the weights of 3230 patients were analyzed. The average maternal weight gain was found to be 23.2 pounds and the average fetal weight gain was found to be 7.4 pounds. Postpartum weight loss, as a rule, approximated by 5 pounds the total weight gain in patients gaining average amounts. Patients whose weight gains were excessive, retained 60 to 80 per cent of this excessive weight, except when it was due to dropsy. The birth weight of the baby was not related to maternal weight gain except when the mother was diabetic or her weight gain was excessive.—*E.C.H.*

WERTENBERGER, GRACE.

The relation of estrin to the basal metabolic rate. Dissertation: University of Chicago, Chicago, 1942.

Following castration and hysterectomy the B.M.R. in 4 dogs fell to levels of −23.1 to −57.8 and in 1 human female to a level ranging from −12.8 to −20.8. The lowering of B.M.R. was accompanied by increase in body weight. Estrone in small dosages (50 I.U. given 6 times over 15 days) stimulated the B.M.R. slightly in the human subject, and heavier dosages (1000 I.U. per day for 6 days) induced a rise to a peak of +8 following an initial fall during the injections. Only 2 dogs showed statistically significant responses, with dosages ranging from 5000 I.U. over 10 days to 50,000 I.U. over 25 days.—*H.O.H.*

WINKLER, A., P. K. SMITH AND H. E. HOFF.

Absence of beneficial effects from injections of desoxycorticosterone acetate and of cortical adrenal extract in experimental anuria. *J. Clin. Invest.* 21: 419. 1942.

Thirty-three dogs were made anuric by ligation of their ureters. Fourteen dogs received various doses of desoxycorticosterone acetate and survived from forty-seven to one hundred and eight hours after the ligation. Their blood N.P.N's rose an average of tenfold. Essentially the same results were found in four dogs which received cortical extract and in fifteen dogs which remained untreated. Since doca is known to alter potassium distribution in normal animals, its failure to act in animals with tied ureters suggests that its action must be upon the kidney.—*B.B.R.*

WINKLESTEIN, L. B.

Prostigmine methylsulfate and delayed menstruation. Evaluation of prostigmine as a test for pregnancy. *Am. J. Obst. & Gynec.* 44: 231. 1942.

Prostigmine methylsulfate has been described as being capable of producing uterine bleeding in women with delayed periods, not caused by pregnancy. Its use has been suggested as a diagnostic test for pregnancy.

Using injections of 1 to 2 cc. of 1/2000 solution of prostigmine methylsulfate daily for 1 to 3 days the effects were studied in 90 women. Fifty-seven of 65 non-pregnant patients bled. Four of 25 pregnant patients bled.—*E.C.H.*

ZONDEK, B., AND B. SHAPIRO.

A simplified method for glycogen estimations in uterine mucosa. *Am. J. Obst. & Gynec.* 44: 345. 1942.

The detail method of a simplified glycogen test for uterine mucosa is described. The test is based on the iodine glycogen color reaction. It is judged to be sufficiently accurate to permit detection of sufficiency or insufficiency of glycogen production by the endometrium.—*E.C.H.*

ADRENALS

DARROW, D. C., AND H. C. MILLER.

The production of cardiac lesions by repeated injections of desoxycorticosterone acetate. *J Clin. Invest.* 21, 601. 1942.

Rats treated with desoxycorticosterone acetate were compared with rats fed on a diet low in potassium and high in sodium. Doca produced cardiac lesions (necrosis of myocardial fibers and replacement by fibroblasts) of sufficient severity to explain cardiac failure. Myocardial injury by doca could be prevented by addition of potassium chloride to the drinking water. No consistent lowering of muscle potassium could be produced by feeding the diets low in potassium whereas doca led to consistent lowering of muscle potassium levels. A similar group of cats failed to respond as consistently as did the rats but some cardiac lesions were produced in four of them. The authors suggest that in the treatment of Addisonian crisis care must be exercised lest excessive amounts of cortical hormone lead to myocardial damage and cardiac failure.—*B.B.R.*

FERREBEE, J. W.

The treatment of Addison's disease with desoxycorticosterone acetate. *Med. Clin. N. America* 25: 1177. 1941.

Desoxycorticosterone acetate has made a potent cortico-adrenal hormone available for the first time to the usual patient with Addison's disease. Desoxycorticosterone in doses of the order of 5 mg. a day produces in human subjects a very considerable decrease in the excretion of sodium, chloride and water, and a moderate increase in the excretion of potassium. Since the usual patient with Addison's disease suffers predominantly from the effects of excessive sodium loss, the ability of this new hormone to regulate sodium excretion makes it a most welcome addition to the therapy of adrenal insufficiency. It does not, however, have significant direct action upon carbohydrate metabolism and should not be considered a complete replacement therapy. Moreover, since amounts greater than those required for the maintenance of normal sodium balance may cause serious complications, it should not be used carelessly or indiscriminately. Individualization is the guide to dosage. A few patients do very well on salt therapy alone and for them the routine use of hormone is probably unnecessary. With other patients, the liberal administration of sodium chloride, 10 to 20 gm. a day by mouth, does not seem productive of results as good as those which can be obtained with the hormone and a normal sodium chloride intake. In this group, daily subcutaneous injections of desoxycorticosterone acetate in oil or the implantation of pellets in amounts sufficient to furnish 1 to 10 mg. of hormone daily are usually sufficient to bring the serum sodium concentration to normal and maintain it at that level. This stabilization of serum sodium concentration is usually attended by marked clinical improvement, increase in strength, increase in appetite, and increase in weight. Once equilibrium is established the patient, in most instances, can be discharged to continue his treatment at home. He should be cautioned, however, that unusual gains in weight, particularly if associated with dependent edema and shortness of breath, are probably indicative of congestive heart failure as a result of overdosage with hormone. Similarly, he should be told that in hot weather or during intercurrent illnesses his requirement of hormone may be increased. Under such circumstances he may need the aid of his physician in adjusting his dosage. This adjustment can usually be accomplished without difficulty by following the blood pressure, water balance, weight, serum protein and serum sodium concentrations and controlling the intake of hormone, fluid and salt in such a manner as to prevent the patient from either bogging down with edema or drying up with adrenal insufficiency. Major adrenal crises require both an intensification of therapy and a sharpening of laboratory and clinical control. Adequate amounts of hormone, saline, glucose, cortical extract, and if necessary blood transfusion, must be given as soon as possible to bring the patient out of shock; but since severely ill Addisonian patients pass very easily into congenstive heart failure, this treatment must be applied with care in order to avoid sudden large increments of blood volume which place too great a strain upon a presumably inadequate myocardium. Therapy may

consist of an immediate divided intramuscular injection of 25 m. mg. of desoxycorticosterone acetate in oil, subcutaneous injection of 25 cc. of a potent aqueous cortical extract, and a slow infusion of 1500 cc. of 5 per cent glucose in normal saline to which has been added another 25 cc. of aqueous cortical extract. Subsequent therapy will depend entirely upon the patient's condition and an evaluation of the laboratory data. The probabilities are that approximately ⅔ of the initial treatment will have to be repeated on the following day; and if the serum protein concentration has fallen to an edema level without evidence of congestive heart failure, increased venous pressure or cardiac silhouette, a serum transfusion may be desirable at that time to help in maintaining the circulating blood volume. In general it may be said that desoxycorticosterone acetate has done, to a certain extent, for Addison's disease what insulin has done for diabetes. It has not cured the disease but it has made it possible to control what is clinically the outstanding physiologic disturbance, namely, an excessive renal excretion of sodium.—*I.B.*

McGavack, T. H.

Optimal dosage and the reciprocal relation of desoxycorticosterone acetate and sodium in Addison's disease. *New England J. Med.* 226: 547. 1942.

In 6 patients with Addison's disease the daily intake of sodium and the daily dose of desoxycorticosterone acetate were varied inversely to one another. Of 47 different ratios tested, 28 proved to be satisfactory, 3 represented states of overdosage and 17 were inadequate. Between the limits of 1.5 to 12 grams of sodium and of 4 to 30 mg. of desoxycorticosterone acetate daily the optimal ratio of these two factors may be expressed by the formula: $Na = 45 \div D$ where Na is the daily sodium intake in grams and D the daily dose in mg. of desoxycorticosterone acetate. Thus if $Na = 9$ then D would have to be 5; were Na reduced to 3, D would have to be increased to 15 and so on.—*E.B.A.*

Talbot, N. B., A. M. Butler and R. A. Berman.

Adrenal cortical hyperplasia with virilism: diagnosis, course, and treatment. *J. Clin. Invest.* 21: 559. 1942.

Nineteen patients were studied to determine whether adrenal hyperplasia could be differentiated from adrenal carcinoma by chemical measurements. Of twelve patients with the diagnosis of adrenal hyperplasia, eleven studied by the present authors, presented evidences of adrenal cortical virilism. Three of the seven reported patients with adrenal cortical carcinoma were studied by the present authors, while four cases were gathered from the literature. Of these seven patients, five presented evidence of adrenal cortical virilism. All patients presenting the adrenal cortical syndrome show elevation of total urinary 17-ketosteroids. The urinary output of alpha alcoholic ketosteroids accounts for the largest part of the total 17-ketosteroid excreted in patients with adrenal cortical hyperplasia. On the other hand the beta alcoholic and non-alcoholic 17-ketosteroid is markedly elevated in patients with adrenal cortical carcinoma. Thus more striking differences between patients with adrenal cortical hyperplasia and adrenal cortical carcinoma are revealed by quantitative analysis of the fractions of 17-ketosteroid than by the total. In confirmation of previous work the authors agree that patients with adrenal cortical hyperplasia should be treated with estrogens while patients with carcinoma should be treated surgically.—*B.B.R.*

Blackmun, R. L.

Ovarian tumor with masculinizing syndrome. *Am. J. Obst. & Gynec.* 43: 1036. 1942.

A virilizing syndrome of a 23 year old woman was reversed by the removal of a left ovarian tumor which was 6.5 cm. in diameter. The cells of this tumor resembled lutein cells. They were large cells with granular cytoplasm which had large nuclei and conspicuous nucleoli. These cells were disposed in irregular strands.—*E.C.H.*

GONADS

Finesinger, J. E., J. V. Meigs and H. W. Sulkowitch.

Clinical, psychiatric and psychoanalytical study of a case of male pseudohermaphroditism. *Am. J. Obst. & Gynec.* 44: 310. 1942.

A case of pseudohermaphroditism was studied clinically, psychiatrically, psychoanalytically and from the hormonal point of view. Structurally the patient was preponderately male. Testes did not produce spermatozoa. There was observed an increased urinary excretion of follicle-stimulating gonadotropin following laparotomy and biopsy of of the testes. This was not observed prior to operation. Urinary androgens were within normal

range. The psychiatric and psychoanalytical studies indicated that the patient had an emotional and psychosexual development typical for females.—*E.C.H.*

GEIST, S. H., AND J. A. GAINES.

Diffuse luteinization of the ovaries associated with the masculinization syndrome. *Am. J. Obst. & Gynec.* 43: 975. 1942.

Two case reports are given. Case 1. A 32 year old negress had had episodes of infrequent and prolonged bleeding and increasing hirsutism since shortly after menarche. There was diffuse trunk and girdle obesity. Clitoris was not enlarged. Both ovaries were twice normal size. These were removed. Obesity and hirsutism persisted. X-ray of sella was normal. Intravenous pyelogram and perirenal air insufflation indicated no adrenal tumor. Case 2. A 27 year old white woman had experienced amenorrhea for 5 years except for several episodes of bleeding during the year prior to her examination. There was progressive hair growth on face and trunk. Voice became deeper. Forty pounds of weight were gained. Obesity was confined chiefly to the face and trunk. The clitoris was four times normal size. X-ray examinations of the sella turcica, an intravenous pyelogram and perirenal air insufflation gave normal findings. The left ovary was enlarged. Both ovaries were removed. The ovaries of both patients upon histologic study were characterized by changes suggestive of increased gonadotropic stimulation: excessive perifollicular proliferation and luteinization of the theca cells and diffusely scattered luteinized cells within the ovarian parenchyma. These ovarian findings were not judged responsible for the virilizational phenomena.—*E.C.H.*

GOODWIN, R. H.

Bilateral ovarian dermoid cysts complicating pregnancy treated by bilateral oophorectomy. *Am. J. Obst. & Gynec.* 44: 525. 1942.

The case of a 25 year old, primigravida, upon whom bilateral oophorectomy was done on the 83rd day following the last menstrual period, is reported. The patient's pregnancy proceeded to term without undue complications, despite the fact that no progesterone therapy was given. Six months after delivery uterine bleeding for 3 days from an atrophic endometrium occurred. The patient's post-partum course was uneventful otherwise except for vasomotor symptoms of surgical menopause.—*E.C.H.*

ISRAEL, S. L.

The clinical similarity of corpus luteum cyst and ectopic pregnancy. *Am. J. Obst. & Gynec.* 44: 22. 1942.

The history, pathogenesis and histology of the corpus luteum cyst are reviewed. Little is known of its etiology: it has been suggested that it may be caused by hypergonadotropic pituitary action.

Five patients, diagnosed preoperatively as having ectopic pregnancies, were found to have corpus luteum cysts. Their cases are reported. Both conditions may have identical symptoms and present the same pelvic signs.

Positive pregnancy tests and decidua-like endometriums may be associated with corpus luteum cysts. The probable mechanisms of these are discussed.—*E.C.H.*

KROHN, L., J. HARRIS AND O. HECHTER.

Sources of error in the detection of ovulation. Correlation of vaginal smear studies with urinary pregnanediol glucuronidate determinations. *Am. J. Obst. & Gynec.* 44: 213. 1942.

This report is concerned with considerations of the theoretic and practical objections to various clinical methods for diagnosing the occurrence of ovulation. The most important objections to the biopsy method are listed. Of the other methods which have been offered, only that employing vaginal spreads and that of estimating urinary levels of pregnanediol-complex are considered worthy of discussion. Certain pitfalls in the interpretation of vaginal smears are discussed. Proper interpretation requires taking daily smears throughout the entire cycle. Artifact peaks of desquamation frequently occur without a corresponding abrupt drop in cornification and do not signify ovulation. Persistently high levels of estrogens may induce a desquamation similar to that produced by progesterone during the luteal phase of the cycle. The supposition that the modifications reported by Venning for pregnanediol glucuronidate determination eliminate most of the impurities in the final product can no longer be considered tenable. A new method for the quantitative determination of pregnanediol glucuronidate based upon the copper reducing activity of the glucuronic acid obtained after acid hydrolysis is referred to and offered as a means of eliminating the sources of error experienced with the method of Venning.—*E.C.H.*

LANGMAN, L., AND H. S. BURR.

Electrometric timing of human ovulation. *Am. J. Obst. & Gynec.* 44: 223. 1942.

The apparatus used in the studies was a Burr-Lane-Nims DC microvoltometer with a General Electric photoelectric recorder as a recording galvanometer. Approximately 150 records were taken from 7 women on the majority of the days of the menstrual cycle. The studies showed that most commonly throughout the menstrual cycle the cervix was positive to the ankle from 5 to 25 MV. In 9 of the 14 cycles studied the cervix became negative, an equivalent amount on at least one day of each cycle. In 4 of these, the cervix remained negative for 2 days. The days of the cycle on which the negativity appeared were the 3rd, 6th, 7th, 8th, 13th, 14th, 18th or the 21st. In 5 cycles either no negative shift occurred or it was equivocal. In 4 patients (cases 1, 2, 3 and 5), despite the fact that in only one did the negative shift coincide with the assumed time of ovulation, artificial inseminations were done but no pregnancies resulted. In the case of patient 5, the negative shift occurred on the 13th and 14th days and was associated with abdominal pain. The case of patient 6 is interesting. The patient's sterility was related to her husband's seminal inadequacy. A negative shift occurred on the 13th and 14th days. At this time an artificial insemination with donor semen was done. Pregnancy resulted. In the case of patient 7 the negative shift occurred on the 6th and 7th days of the cycle. Artificial insemination was done at this time. Subsequently menstruation was delayed 11 days. The authors are of the opinion that since it was possible to secure at least one positive correlation, it should prove worth while to extend the study to as many patients as possible. They suggest also that a study of the effects of hormonal injections upon the electrical record would be advisable. As an addendum to the article, there are 2 more case reports. One of these patients became pregnant following donor artificial insemination done at the time of negative shift.—*E.C.H.*

MACBRYDE, C. M.

Synthetic estrogens: their future: therapy of hypogonadism with stilbestrol. *J. Kansas M. Soc.* 43: 281. 1942.

Women (150) were given diethylstilbestrol dipropionate intermittently or continuously over a period of at least 3 months. Symptoms included those of spontaneous menopause, artificial menopause, and eunuchoidism with amenorrhea and primary hypogonadism. Two criteria were required for treatment: symptoms severe and characteristic of hypo-estrinism, and vaginal smears of the castrate type. A progressive reduction in dosage, by change from continuous to intermittent treatment, relieved a tendency toward nausea. There was no evidence of toxicity in the dose levels used. Striking improvement occurred with respect to vasomotor and emotional instability, headaches and insomnia. Pruritis vulvae was relieved in 20 of 26 cases. Increased libido and improved sex relations were reported by 31. General improvement in strength and energy occurred in 84 of the 97. Satisfactory dosage levels were obtained with 1 mg. daily for alternate two-week periods.—*E. Huene* (*Biol. Abst.*).

MARX, R., S. GLASS AND A. SHULMAN.

Experimentally produced fibroids in the guinea pig and their possible analogy to myomas in the human being. *Am. J. Obst. & Gynec.* 44: 259. 1942.

The authors have been able to produce fibromyomatous tumors in the guinea pig by prolonged estrogenic therapy, thus confirming the results of the extensive studies of Lipschütz and his co-workers.

They observe that in spite of the histologic differences certain analogies can be found between the genesis and production of experimental fibroids and human myomas. Both types of tumors arise from mesoblastic cells: the guinea pig tumors seemingly from undifferentiated connective cells and the human myomas from immature muscle cells. The growth of both types of tumors seems to depend upon estrogenic action when this is not counterbalanced by other growth-controlling catalysts.—*E.C.H.*

MURRAY, N. A., M. B. DOCKERTY AND J. DE J. PEMBERTON.

Unusual coexistence of granulosa cell tumor and ovarian teratoma containing thyroid tissue. *Am. J. Obst. & Gynec.* 44: 134. 1942.

The record of a patient, 56 years old, para 1-0-1, who experienced post-menopausal bleeding and apparent rejuvenation in association with pelvic tumors is described. The tumors identified by surgery and pathologic studies included a dermoid cyst of one ovary and associated thyroid tissue, granulosa cell tumor of the other ovary and multiple leiomyomas of the uterus.—*E.C.H.*

REA, C. E.

Present day concepts of the undescended testis with special reference to endocrine therapy. *Internat. Clin.* 4: 262. 1941.

Undescended testis occurs about once in every 500 males. The cause is unknown. While, with the onset of puberty, spermatids have been seen in the retained gonads, spermatozoa have never been seen. Pain, torsion, hernia and malignancy are the most common complications of testicular maldescent. Except for hernia, however, most patients with cryptorchidism do not seek treatment because of a complication, but are concerned about the aberrant position of the gland. Only 2 or 3 per cent of undescended testes become malignant. While the undescended testicle is often aspermatic, the gland nevertheless secretes an internal hormone as proved by the capon comb test. Most evidence indicates that the undescended testicle will develop normally when replaced in the scrotum, but if too far degenerated, mature germinal epithelium will not be produced subsequent to fixation in the scrotum. Treatment is either surgical or by hormonal injections. But an evaluation of any treatment must take into account the percentage of testicles that will descend spontaneously. Most observers believe that spontaneous correction occurs in more than 50 per cent of cases. Moreover, instances of pseudocryptorchidism, which usually undergo spontaneous descent at puberty, must be accounted for in statistical data. Surgical treatment of the cryptorchid consists of removal, abdominal reposition, or scrotal fixation. Castration is justified only in certain cases of unilateral undescended testis: (1) if the patient is old and has a very atrophic testis or a large inguinal hernia, (2) if the testis is painful, or (3) if the presence of a malignant tumor is suspected. From an anatomic and physiologic point of view, orchiopexy is the procedure of choice in the surgical treatment of the undescended testis. It is important that the testis after orchiopexy be free in the bottom of the scrotum and be movable. It has been the practice at the University of Minnesota clinic to wait until puberty before treating uncomplicated cases of retained testis. At present, anterior pituitary-like substances in doses of 500 rat units per cc. are injected every day or every other day for 10 injections in cases of ectopy. If no results are obtained the patient is given 1 month's rest and then a similar course of therapy instituted. If no results are obvious the patient is allowed a rest of 3 to 6 months and an orchiopexy performed. No untoward effects from the use of gonadotropic substances have been observed in the doses used. It is interesting to note that in every case upon which an orchiopexy has been performed at this clinic, evidence of mechanical obstruction to the descent of the testis (short cord, adherence of testis to hernial sac, adhesions and bands) has been present. To give a final estimate of the value of gonadotropic substance in the treatment of ectopic testis is impossible at this time. The incidence of spontaneous descent is not accurately known. Furthermore, it must be determined whether endocrine therapy causes descent only of those testes which would descend without therapy about the time of puberty. The chief value of endocrine therapy is that it makes it possible to differentiate between those testes which require surgical intervention because of mechanical obstruction to descent and those which do not. Treatment of the retained testis should be deferred until the patient is 9 to 11 years of age since the testis does not grow grossly or microscopically until then, and since it is possible that spontaneous descent may occur. A course of endocrine therapy should be given first to see if the additional hormonal stimulation will cause the gonad to descend into the scrotum. If no results are obtained, an orchiopexy should be performed.—*I.B.*

SCHWARZ, J.

A study of excretion of gonadotropic hormone in benign prostatic hypertrophy. *J. Urol.* 48: 170. 1942.

In view of the facts that prostatic enlargement occurs in those age groups when gonadal activity begins to decline and declining or absent gonadal function in the female is accompanied by an increase in activity of the pituitary gland, a study was undertaken to determine whether pituitary stimulation occurs also in the normal male of advanced years and in the patient with prostatic hypertrophy. Determination of the content of gonadotrophic hormone in the urine was done by bioassay after the Frank modification of the Zondek alcohol precipitation method. Immature female rats, 30 to 35 gm. were used, employing ovarian responses as the criterion of hormone activity. Pooled 3-day specimens were assayed for both FSH and LH. Seven patients with benign prostatic hypertrophy, and 1 patient with carcinoma of the prostate, were studied. No increased secretion of the hormone over normal controls of the same age could be demonstrated.—*E. Neter. (Biol. Abst.).*

HYPOPHYSIS

HAM, G. C. AND E. M. LANDIS.

A comparison of pituitrin with the antidiuretic substance found in human urine and placenta. *J. Clin. Invest.* 21: 455. 1942.

The material was prepared from 12 hour urines of patients with hyperemesis gravidarum, hydatid mole, preeclampsia, and eclampsia. The urines were cooled, dialized, and concentrated to such a volume by boiling in vacuo, that 1 cc. was the urine excreted in 15 to 25 minutes. Urine from one dehydrated subject, from 3 normal subjects, and from hydrated and dehydrated rats was similarly treated. Antidiuretic activity was assayed by a modification of Burn's rat method. The results on the rats confirmed those previously reported by other investigators, and are similar to those in normal hydrated and dehydrated humans. Normally hydrated humans showed no increase in antidiuretic substance, while a normal dehydrated subject showed a moderate increase in antidiuretic substance. Patients with toxemias of pregnancy all showed increased antidiuretic substance. A similar substance could be found in extracts from placentas of 5 patients delivered in the course of a toxemia, while none was found in the extracts of 6 patients with normal deliveries. This antidiuretic substance differs from pituitrin in not causing chloride excretion. Unlike pituitrin it can be concentrated by ultracentrifugation. It dializes slowly through cellophane.—*B.B.R.*

MURPHY, D. P.

The relation between uterine activity and reactivity to posterior pituitary extract during pregnancy. A study of 656 records made with the Lóránd Tocograph. *Am. J. Obst. & Gynec.* 44: 117. 1942.

The frequency of occurrence of uterine contractions arising spontaneously, and of those contractions induced by the intramuscular administration of posterior pituitary extract, was studied in a group of 232 pregnant women, between the 110th and 279th days of gestation by means of the Lóránd tocograph.

The proportion of records registering activity and reactivity increased progressively as pregnancy advanced, running parallel to each other.

It is concluded that the sensitivity of the human uterus to posterior pituitary extract increases progressively as pregnancy advances.—*E.C.H.*

SCOTT, R. B., AND P. T. JOHNSON.

Laurence-Moon-Biedl Syndrome. Its occurrence in a Negro child; treatment with gonadotropin and androgen. *Am. J. Dis. Child.* 63: 733. 1942.

The patient was a Negro boy of 12 years of age who presented a picture of obesity, hypogenitalism, mental deficiency, defective vision, polydactylism and impaired hearing. No improvement was noted in the vision or mentality on endocrine therapy. The cryptorchidism responded to treatment with testosterone propionate but not to chorionic gonadotropic hormone.—*M.B.G.*

PANCREAS

BIRNKRANT, W. B.

The influence of a parotid extract on the blood sugar and structure of the pancreas of the rat. *J. Lab. & Clin. Med.* 27: 519. 1942.

The author prepared alkaline extracts of beef parotid glands which upon injection into the rat elevated the fasting blood sugar. While the reaction to a single injection is completed within 24 hours, repeated injections lead to maintained elevations of blood sugar and to the production of glucose tolerance curves resembling those of human diabetics. Autopsies on rats receiving repeated injections revealed slight changes in the islets of Langerhans, a few of which exhibited varying degrees of degeneration. Control injections with beef broth showed no comparable changes either in blood sugar elevation or in pancreas morphology.—*B.B.R.*

COLLEN, M. F.

Mortality in diabetic coma. *Arch. Int. Med.* 70: 347. 1942.

The author's study of the various factors influencing the mortality in 315 cases of diabetic coma occurring in 274 diabetic patients at the Los Angeles County General Hospital yields the following conclusions: Mortality statistics in diabetic coma are of no value unless attacks of coma of equal severity are compared. Coma occurs more frequently during the puberal and the climacteric decades. Mortality is equal in the 2 sexes. In the great majority of cases death in diabetic coma is due to shock or associated complicating disease. One-half of all fatalities in coma occur between 6 and 24 hours after admission to the hospital. Fifty-four per cent of this series of comas were precipitated by infections, es-

pecially of the respiratory tract. Insulin insufficiency was the second most common precipitating cause of coma, due either to complete cessation of insulin administration or to insufficient dosage. Factors of greatest importance and of fundamental nature influencing the mortality of diabetic coma are (a) the age of the patient, (b) the diastolic blood pressure, (c) the degree of unconsciousness and (d) complicating diseases. Factors of lesser importance in estimating severity of diabetic coma are (a) duration of coma, (b) blood nonprotein nitrogen and (c) blood sugar. There is no relation between the carbon dioxide-combining power of the blood and mortality. A modified index of severity contained in the body of this contribution is recommended for use in estimating severity of diabetic coma. A severity formula is also described, which indicates severity of coma and allows one to predict average prospective mortality. In this series, coma occurred twice in 16 patients, 3 times in 5 patients, 4 times in 1 patient and 7 times in 2 patients.—*I.B.*

COLLEN, M. F.

Interrelation of the factors influencing mortality in diabetic coma. A statistical study. *Arch. Int. Med.* 70: 369. 1942.

A study of 315 cases of diabetic coma at the Los Angeles County General Hospital has brought out several factors which influence the mortality of diabetic coma. The author summarizes his deductions as follows: The increasing mortality with age is primarily due to the increased number and the increased severity of complications in older age groups. The degree of unconsciousness of a patient in diabetic coma varies with blood pressure, blood sugar, the carbon dioxide-combining power of the blood, age and severity of the complicating disease in decreasing importance. The high mortality in severe degrees of unconsciousness is predominantly due to the presence of increased frequency and severity of complications and severe shock. Duration of coma is of secondary importance; however, patients in diabetic coma who are untreated for over 48 hours and who are still alive form an interesting small group who seem to tolerate acidosis well and have only moderately severe coma. The degree of shock varies with the degree of unconsciousness and the values for blood nonprotein nitrogen and blood sugar. The degree of azotemia primarily varies with the blood sugar and the blood pressure and to a lesser extent with the degree of unconsciousness, age and the carbon dioxide-combining power of the blood in the order named. The high mortality in severe azotemia is probably due to associated shock, there being a direct relation between diastolic blood pressure and blood nonprotein nitrogen. The carbon dioxide-combining power of the blood decreases with rising bloood sugar and increasing depth of unconsciosuness. The degree of hyperglycemia is influenced by diastolic blood pressure and to a lesser extent by the degree of unconsciousness. Although the presence of a complicating disease is an important factor influencing the mortality of a patient in coma, it does not appear to influence the level of blood sugar or blood nonprotein nitrogen or the carbon dioxide-combining power of the blood.—*I.B.*

DRURY, D. R.

The significance of the D:N ratio and its bearing on the mechanism of diabetes mellitus. *J. Clin. Invest.* 21: 153. 1942.

Three dogs, fasted for 4–5 days, received daily injections of 1 gram phlorhizin in oil. Their fasting D:N ratios approached 3.5. When fed from 450 to 1300 grams of lean meat the D:N ratio diminished. Three depancreatized dogs maintained on 5 units of insulin per day were fed various quantities of lean meat or fat free meat powder, and on other days fed pure sugar. In these animals the D:N ratios after correction for carbohydrate utilization approached 5.5. It is suggested that with this high D:N ratio both the glucose excreted and the glucose utilized by the tissues can be accounted for on the basis of the protein breakdown.—*B.B.R.*

ASSOCIATION NOTICE

ANNOUNCEMENT

EDITORIAL CHANGES, ENDOCRINOLOGY

Dr. E. B. Astwood and Dr. E. W. Dempsey, of the Harvard Medical School, have been appointed Managing Editor and Associate Managing Editor, respectively.

They will have the collaboration of a newly established Editorial Board consisting of Drs. J. S. L. Browne, E. T. Engle, C. G. Hartman, E. C. Kendall, F. C. Koch, C. N. H. Long and H. B. van Dyke.

These changes will become effective with the February issue.

NOTICE

UPON ADVICE of the Office of Defense Transportation, the meeting of the Association for the Study of Internal Secretions tentatively scheduled for April 5th and 6th at Cleveland, Ohio is indefinitely postponed.

E. K. SHELTON, *President*